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THE DIAGNOSTIC AND THERAPEUTIC VALUE OF LIVER BIOPSIES*

With Particular Reference to Trocar Biopsy

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ACCURATE information regarding the particular phase of any morbid process under observation is essential to the institution of adequate therapeutic measures. Such an obvious and desirable goal, until recent years, has been only vaguely obtainable in intrahepatic disease. Numerous liver-function tests of simple or complex nature have been devised but have proved useful primarily as a means of estimating the degree of functional damage and of following the progress of intrahepatic disease rather than as a measure of exact diagnosis. The multiplicity of the liver's functions and its notable reserve capacity are such that at best, even when the entire battery of laboratory studies is employed, an imperfect set of findings is obtained. This statement is not to be interpreted as underestimating the various tests of hepatic function, which have a distinct but limited value.

For these reasons various investigators have made an effort to obtain exact histologic information by means of liver biopsy. We also have been interested in a careful histopathologic study of liver disease and have found, as others have, that such knowledge is frequently vital in making correct clinical decisions regarding the differentiation of intrahepatic and extrahepatic biliary obstruction, the type of intrahepatic disease present, the stage of a known intrapehatic disease, the specific therapeutic program to be followed and the appraisal of a therapeutic regime. To justify the practice of liver biopsy, it is necessary to satisfy the following conditions: the procedure must present no undue risk to the patient, and the material so obtained must be adequate for careful histologic examination.

In general, all three of the present-day methods (laparotomy with small incision under local anesthesia, peritoneoscopy and needle biopsy) fulfill both these requirements. Laparotomy is usually unjustified if either of the two other procedures is available, since the discomfort to the patient is as great as that in the usual peritoneoscopy and the abdominal-wall incision is necessarily much larger. The area of hepatic tissue grossly visualized in such a laparotomy is, of course, considerably less than that seen through the peritoneoscope. In terms of time and money, the expense to the patient is greatest for laparotomy and least for trocar biopsy.

Peritoneoscopy is a painful procedure, and it is therefore difficult to induce a patient to have a second or third examination to obtain material useful in following the progress of intrahepatic disease. In diffuse liver disease, a peritoneoscopic biopsy is often inadequate in its sampling of tissue, and when there has been intrahepatic scarring, the specimen may consist chiefly of liver capsule. Peritoneoscopy should be chosen as a rule when a search for a focal lesion — for example, a neoplasm — is necessary. Even in diffuse intrahepatic disease, gross visualization of the liver at times adds important information to that obtained histologically; often, this can all be accomplished by a single peritoneoscopic examination. This procedure also enables the operator to coagulate electrically the site of biopsy if much bleeding is seen. The use of an exterior biopsy needle combined with peritoneoscopy[1, 2] seems unnecessarily elaborate except in unusual circumstances.

Needle biopsy of the liver, when properly performed, usually causes little discomfort and, if a fairly uniform pathologic process is present, provides a satisfactory sampling of tissue from deep within the liver substance. The development of this method has previously been adequately discussed.[3–8] If the liver is markedly enlarged, an attempt to obtain a specimen of suspected metastatic neoplasm by needle biopsy is often reasonable, but failure to find it by this blind method in no way rules out that diagnosis. In coarsely nodular, "toxic cirrhosis," a needle biopsy may fail to include scar tissue although the specimen is seemingly sufficient in amount. Trocar biopsy of a liver that is

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considerably smaller than normal is, in our experience, uncertain and unsafe, nor should a biopsy needle be thrust blindly across pleural or peritoneal planes when focal suppuration is suspected. Chronic passive congestion of the liver may contraindicate liver biopsy, although we have obtained without untoward incident a trocar biopsy in 4 such cases and Sherlock[7] reports 25 cases.

Method

Experience has indicated that, if proper biopsy material is to be obtained consistently, a special kind of needle is necessary. Of the various types of biopsy needles used at present, one is about as satisfactory as another if the operator is experienced and skillful. For the study of most hepatic disorders, we have chosen to use an American modification of the Iversen–Roholm needle, known as the Franseen biopsy needle,* because it seems to be the simplest effective apparatus available for this purpose. It differs from the original one described by Iversen and Roholm[9] only in that the three sharp points have been fully developed into three sharp teeth. We use the No. 14 gauge size, 11 cm. in length.

The biopsy is performed at the bedside with the patient lying flat on his back; the anterior approach is used. The skin is prepared with alcohol and iodine, and a sterile sheet with a central hole is placed over the chosen area. After a skin wheal has been made with novocain, the thoracic or abdominal wall down to and including the peritoneum is rapidly anesthetized while the patient holds his breath in the phase of respiration chosen for the biopsy. A 0.3-cm. skin nick is made with a sharply pointed Bard–Parker blade. The patient hyperventilates a few times and holds his breath while the biopsy is being done. The biopsy needle, stylet in place, is quickly pushed through all layers of the abdominal wall to the surface of the liver capsule. The stylet is withdrawn and the needle shaft rapidly advanced within the liver substance for a vertical distance of 3 or 4 cm. Suction is then applied to the end of the needle with a 20-cc. syringe having a metal adapter. With the suction in place, the needle and syringe together are quickly withdrawn. As this is done, the tissue obtained usually slides up the needle shaft into the barrel of the syringe, and immediately 10 cc. of physiologic saline solution is aspirated into the syringe to prevent a blood clot from forming around the biopsy specimen. The tissue is then transferred to the fixative.

The actual biopsy maneuvers must be accomplished within ten seconds to allow the patient to hold his breath and lie immobile; otherwise, a liver tear is possible. Overbreathing to achieve a period of spontaneous apnea helps the patient fulfill this requirement. We believe that there should be no fixed rule concerning the site of biopsy, which should be chosen by the operator in each case according to the physical examination. By the anterior approach, if the liver is enlarged, either the right or the left lobe may be chosen, provided a 5-cm. margin of safety lies between the site of biopsy and the lower liver edge. If the lobe is sharp-edged and thin, the needle should be pointed obliquely cephalad to prevent puncture of organs on the opposite side. An appreciable ascites should be tapped prior to the procedure. If the liver is only minimally enlarged or is of normal size, it is unsafe to attempt biopsy below the costal margin. In such a case, one may proceed with care transpleurally in the anterior axillary line through the intercostal space during expiration. The space usually chosen by us is the first or second below the top level of liver dullness. We prefer to risk going too high rather than too low since, if the patient is immobile, no harm results from puncturing the lower thin edge of lung.

The patient must be alert and co-operative. The prothrombin time must be carefully checked and should be within normal limits or only slightly prolonged. In unusual cases, a freshly drawn, citrated whole-blood transfusion may be given just prior to the biopsy to reduce temporarily an elevated prothrombin time that has been resistant to parenterally administered vitamin K derivatives. An intramuscular injection of one of these derivatives should be given routinely two hours before the biopsy; regular prebiopsy cross matching for possible later transfusion seems unnecessary.

Pain following needle biopsy is highly variable and unpredictable. It is undoubtedly due to irritation of the serous surfaces by extravasated blood. Biopsies done by the trocar method under direct observation at laparotomy produce from 5 to 20 cc. of blood from normal livers. Pleural pain is almost always present after the use of the intercostal approach, but it is usually not severe after the first half hour. It is considered wise to give parenteral Demerol and an oral salicylate routinely half an hour before the biopsy. The patient should lie quietly in one position for the first hour following the procedure, and should stay in bed for the subsequent twenty-four hours. The return of pain after ambulation is a warning sign of probable further oozing of blood from the biopsy site, and if this occurs the patient should immediately return to bed for at least twenty-four hours longer.

Results

We have attempted needle liver biopsy by this method 234 times in 191 different patients. Of these, 216 biopsies, obtained from 174 patients, provided tissue sufficient for adequate histologic appraisal. In 5 cases focal lesions were missed by an apparently satisfactory biopsy. Sixty-eight biopsies were performed transthoracically in patients with livers of normal size. Thirty-two patients were examined serially with from 2 to 6 biopsies each during the course of therapy. The distribution of pathological

*Manufactured by Randall-Faichney Corporation, Boston.

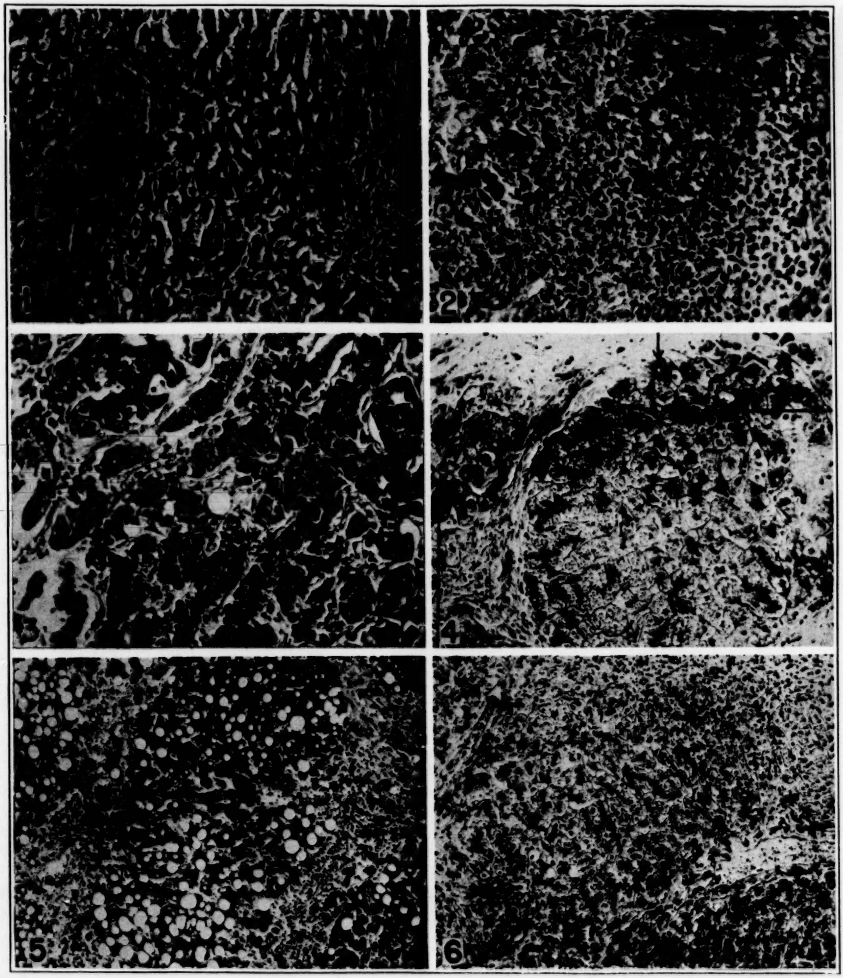

PLATE 1.

FIGURE 1. *Case 1.*

Note the lymphocytic infiltration of the portal areas characteristic of epidemic infectious hepatitis.

FIGURE 2. *Case 2.*

Malignant lymphoma infiltrating the liver lobule.

FIGURE 3. *Case 3.*

Adenocarcinoma suggestive of hepatoma.

FIGURE 4. *Case 4.*

Iron stain, showing intracellular hemosiderin granules of hemachromatosis.

FIGURE 5. *Case 5.*

Acute degenerative cirrhosis. Note the marked fat vacuolization of the parenchymal cells and the severe leukocytic infiltration.

FIGURE 6. *Case 5.*

Biopsy obtained 3 weeks later than that shown in Fig. 5. Note the normal appearance of the parenchymal cells with disappearance of fat and the marked decrease in polymorphonuclear infiltration.

diagnoses in this series is shown in Table 1. Most of the unsuccessful biopsy attempts occurred in patients with ascites that had not been tapped, or in cases of far-advanced fibrosis in which the suction was apparently insufficient to extract the laterally severed tissue from its base.

One death from uncontrolled hemorrhage followed trocar liver biopsy. In this case the biopsy of a large amyloid liver was accomplished with ease while the patient lay immobile; Hykinone had been given parenterally before biopsy. The prothrombin time was 6 seconds prolonged, which is the arbitrary limiting value chosen by us for this procedure. Ten hours later the patient was found in shock after several hours of severe abdominal pain. Post-mortem examination two days later showed that the needle had pierced the right main hepatic vein 4.5 cm. from the surface of the capsule. Intrahepatic bleeding appeared to have created enough pressure to split the friable, superficial amyloid liver tissue, forming a huge laceration extending the entire vertical length of the right lobe. This rent had extended much farther during the twenty-four hours after fibrin foam packing at surgical laparotomy.

One patient died with peritonitis that was possibly attributable to the biopsy procedure. This man, with a fulminating acute cirrhosis, was found at autopsy to have a beta-hemolytic streptococcus peritonitis and septicemia. The pathologist stated that this infection appeared to be of three to ten days' duration. The temperature chart and clinical data provided no clue to the time of its onset. The biopsy had been performed five days before death. Since this experience, all biopsy instruments have been carefully autoclaved as complete sets. We believe, however, that this death was not attributable to aspiration biopsy.

Moderate bleeding after biopsy was observed in 3 other patients, in all of whom the prothrombin time was normal; none required transfusion. Two patients bled intra-abdominally, accumulating a detectable ascites, and 1 developed a large abdominal-wall hematoma without intraperitoneal bleeding. One of those with intraperitoneal bleeding had a highly vascular metastatic carcinoma; the other had shown a slight hemorrhagic tendency, not related to platelet or vitamin C lack, but had been given a fresh whole-blood transfusion just before the biopsy.

Case Reports

The following cases illustrate the value of liver-biopsy material in providing correct diagnoses, in determining the phase of a given hepatic disorder actually present and in appraising the results of a therapeutic program in patients with diffuse liver damage.

Case 1. A thin, tired 48-year-old man was hospitalized for study of painless, pruritic, deep jaundice that had been present for 3 weeks. This had been preceded by 3 months of increasing fatigue and a weight loss of 20 pounds without gastrointestinal symptoms. No history of alcoholism was obtainable. The jaundice had been accompanied by light stools and dark urine. A slightly enlarged, nontender liver was palpable. No splenomegaly, spider angiomas or abnormal fluid retention was demonstrable. X-ray films of the chest and upper gastrointestinal tract were normal. During the 1st week of hospitalization the stool varied irregularly from clay colored to light brown. One stool was strongly guaiac positive. Two sets of blood chemical studies a week apart were almost identical in values, including a total serum bilirubin of 40 mg. per 100 cc., a serum alkaline phosphatase of 9 Bodansky units and a total cholesterol of 255 mg. per 100 cc., with normal figures for prothrombin, thymol turbidity and flocculation, cephalin flocculation, albumin and globulin.

Table 1. *Diagnoses Revealed by Trocar Aspiration Liver Biopsy.*

Diagnosis	No. of Patients	Diagnosis Determined by Biopsy
Fatty infiltration	15	12
Portal cirrhosis	57	5
Hemachromatosis	4	4
Bile stasis	12	6
Biliary cirrhosis	5	2
Infectious hepatitis, acute	16	1
Infectious hepatitis, chronic	10	2
"Arsenical" hepatitis	2	0
Hepatoma	4	4
Metastatic carcinoma	9	9
Malignant lymphoma	1	1
"Aleukemic" leukemia	1	1
Amyloid infiltration	2	2
Chronic passive congestion	2	0
Sarcoid	2	2
Normal liver, clinically thought abnormal	22	22
Miscellaneous*	7	6
Totals	171	79

*Includes 1 case of central necrosis, 1 of focal degeneration, 2 of unclassifiable hepatitis, 1 of carbon tetrachloride hepatitis, 1 of schistosomiasis and 1 probable case of cardiac cirrhosis.

Because metastatic carcinoma was strongly suspected, a peritoneoscopy was performed. No focal lesions were seen. The specimen obtained on liver biopsy was typical of epidemic infectious hepatitis, which had not been suspected from the clinical and laboratory data (Fig. 1). In this case, an exploratory laparotomy that might have impaired or greatly retarded the patient's recovery was avoided.

Case 2. A drowsy, well nourished, 69-year-old man presented a history of an acute painless illness of 3 weeks' duration, initiated by abdominal distention and vague indigestion. This was followed in 2 weeks by nausea, vomiting, fatigue and dark urine. Three days before entry frank jaundice had appeared.

Moderate icterus and a large, symmetrical, slightly tender liver were the only abnormal physical signs present. The stools were brown.

Laboratory studies included a cephalin-flocculation test, which was +++ in 24 hours, a serum alkaline phosphatase of 12 Bodansky units per 100 cc. and a positive test for urinary urobilinogen in a dilution of 1:512.

Some observers believed this to be a fulminating acute epidemic infectious hepatitis, superimposed on a large, fatty or cirrhotic liver, although no reliable history of alcoholic intake could be extracted. Others held that such a tremendous, firm liver ought to be filled with neoplasm. A needle biopsy of the liver demonstrated a malignant lymphoma (Fig. 2).

At post-mortem examination, this process was seen to be localized to the liver, vertebral bone marrow and mesenteric lymph nodes. A correct ante-mortem diagnosis could have been made only by liver biopsy.

CASE 3. A cachectic, 63-year-old man had been seen in the outpatient clinic 6 weeks before admission complaining of migratory bone and joint pains. A careful and complete physical examination at that time had been negative. X-ray films of the chest and various bones were normal. Two weeks before entry, there was a rapid onset of ankle edema, chest and back pain and alternate constipation and diarrhea.

Physical examination showed fluid in the right pleural cavity, ascites, peripheral edema and hepatomegaly. X-ray films of the colon, upper gastrointestinal tract and kidneys were normal. It was assumed that widespread metastatic neoplasm was present. A peritoneoscopy was performed by Dr. Edward B. Benedict, whose report was as follows:

> The surface of the left lobe is smooth, with a slightly rounded edge and a 0.5-cm. lesion on the lower part of the anterior surface. This lesion may be metastatic carcinoma but could be fibrosis. The right lobe is smaller than the left, a little more irregular and slightly granular, with a more rounded edge. There are no areas on the surface suggesting carcinoma. In the lower portion of the abdomen on the peritoneal surface of the abdominal wall there are three or four gray-white, irregular areas about 1 cm. in diameter that look fibrotic but may be metastatic carcinoma. None of them are sufficiently large or accessible enough for biopsy.

In a biopsy specimen taken from the anterior surface of the left lobe of the liver, the capsule is extraordinarily tough, and it is quite possible that little liver tissue was obtained. It was impossible to take the biopsy from the small lesion where carcinoma was suspected because this area could not be found with the small telescope. The findings are inconclusive. From the size of the liver and the appearance of it, there may be carcinoma inside the capsule that has not yet broken through and is therefore not visible by peritoneoscopy, although there is a slightly suspicious area.

The biopsy so obtained consisted of a small island of normal liver cells.

A few days later a trocar biopsy was obtained from both the right and the left lobes of the liver; each specimen consisted almost entirely of carcinoma, interpreted by the pathologist as suggestive of hepatoma (Fig. 3).

It is unusual for a blind needle biopsy to yield neoplastic tissue when the peritoneoscopy has failed to obtain it.

CASE 4. A 45-year-old man developed progressive hepatic enlargement during the 2 years subsequent to a transient episode of icterus that occurred during antisyphilitic arsenical therapy. He was a frequent imbiber of alcohol.

Physical examination revealed diabetes, a large liver and a slight tan tint to the skin. Splenomegaly, edema, icterus and spider angiomas were absent.

Laboratory data included a negative cephalin-flocculation test, a total serum protein of 6.8 gm per 100 cc., with an albumin of 3.2 gm., a globulin of 3.6 gm. and an alkaline phosphatase of 3.2 Bodansky units per 100 cc. The bromsulfalein test showed 22 per cent retention of the dye in 45 minutes after a dose of 5 mg. per kilogram of body weight. The blood electrolytes were normal; a test for follicle-stimulating hormone was positive for 6.5 mouse units in 24 hours, and that for 17-ketosteroid urinary excretion showed 1.8 mg. in 24 hours.

X-ray films revealed no esophageal varices. A skin test with acidified potassium ferrocyanide solution and two skin biopsies were negative for hemachromatosis. A trocar liver biopsy showed definite hemachromatosis (Fig. 4).

The patient returned to the hospital 1 month later in cardiac failure and died, and autopsy disclosed hemachromatosis of the liver, pancreas, adrenal glands, lymph nodes, thyroid gland, pituitary body and heart. Esophageal varices were also present.

Liver biopsy was essential for a correct clinical diagnosis in this case.

CASE 5. A middle-aged man was admitted to another hospital* because of chronic alcoholism of 3 years' duration. For the 3 weeks before entry he had ingested little food but considerable alcohol. When completely sober, he maintained that he had no symptoms of any physical illness whatsoever, although the liver was large and the scleras slightly icteric. He was afebrile.

Laboratory data revealed a trace of bilirubinuria and urine urobilinogen detectable in a 1:1500 dilution. The bromsulfalein test showed 36 per cent retention of the dye in 45 minutes after a dose of 5 gm. per kilogram of body weight. The serum bilirubin was 0.8 mg. per 100 cc. direct and 1.5 mg. indirect. The values for serum albumin, globulin, prothrombin, vitamin A, cephalin flocculation and thymol turbidity and flocculation were normal.

A trocar liver biopsy obtained was described as follows:

> There is severe diffuse cirrhosis with unusually marked polymorphonuclear infiltration. Fat vacuolization is of moderate severity and irregularly distributed. The vacuoles are of exceptional size. In a few areas hyaline degeneration is evident (Fig. 5).

This severe, acute, degenerative process had been unsuspected by careful clinical and laboratory examinations. Because of the histologic information, the patient was kept under close medical observation and given intensive dietary therapy. A second biopsy was obtained 3 weeks after the first, at which time the liver was only slightly smaller. The patient was still minimally icteric, although bile pigment had disappeared from the urine. The urinary urobilinogen had returned to a normal concentration; the other liver-function tests were essentially unchanged. Histologic comparison of this biopsy with the first showed a marked reparative change to have taken place:

> The fat has largely disappeared. The majority of the liver cells now appear normal, whereas few did so in the original biopsy. Polymorphonuclear cells are still present, but markedly decreased in number. The fibrosis remains unchanged (Fig. 6).

In the following patients with similar clinical histories, physical findings and laboratory tests, histologic studies of the liver were markedly different. On physical examination the livers were

TABLE 2. *Laboratory Data in Cases 6, 7 and 8.*

CASE NO.	SERUM BILIRUBIN		BROMSULFALEIN RETENTION*	CEPHALIN FLOCCULATION		SERUM ALBUMIN	SERUM GLOBULIN	ALBUMIN-GLOBULIN RATIO
	DIRECT mg./100 cc.	INDIRECT mg./100 cc.	%	AT 24 HR.	AT 48 HR.	gm./100 cc.	gm./100 cc.	
6	0.9	1.3	50	++++	++++	2.31	3.50	0.65
7	Normal	Normal	34	+	+++	2.58	4.30	0.60
8	0.6	1.2	32	+++	++++	2.95	5.38	0.55

*Forty-five minutes after administration of 5 mg. per kilogram of body weight.

In the following patients with similar clinical histories, physical findings and laboratory tests, histologic studies of the liver were markedly different. On physical examination the livers were

*This patient was examined through the courtesy of Dr. Joseph Thimann, medical director of the Washingtonian Hospital, Boston, an institution devoted to the treatment of male alcoholic patients.

approximately of the same size, and icterus was not evident. The laboratory data in these cases are presented in Table 2.

CASE 6. A 46-year-old man was admitted to the hospital because of a rapid onset of ascites within a few days. For many years the alcoholic intake had been impressive, and the food intake scant and irregular. Ankle edema had been present intermittently for 6 months.

Physical examination revealed spider angiomas, ascites, ankle edema, splenomegaly and an enlarged, firm liver.

A liver trocar biopsy obtained shortly after admission was described as follows:

> A definite cirrhosis without fat vacuolization is seen. Many liver cells show pyknosis. Hyaline bodies thought to represent remnants of necrotic liver cells are present. There is moderate lymphocytic infiltration of the portal areas.

This fibrotic inflammatory picture was not considered characteristic of either the usual and expected degenerative cirrhosis associated with malnutrition and alcohol or the epidemic infectious hepatitis due to a virus. A satisfactory pathological classification was impossible.

CASE 7. A 35-year-old Italian housewife was admitted because of anorexia, weakness and abdominal swelling of 3 months' duration. For many months the food intake had been exceedingly poor in quality and small in quantity. The regular daily intake of wine had progressively increased.

Physical examination demonstrated a minimal ascites, a large liver and a palpable spleen.

Needle liver biopsy obtained shortly after admission was reported as follows:

> The architecture is obliterated, and there is definite cirrhosis. There is abundant fat, a small amount of hyaline degeneration and scattered focal necroses with considerable polymorphonuclear reaction.

This was considered typical of the acute inflammatory, degenerative cirrhosis usually associated with malnutrition and alcohol.

CASE 8. A 45-year-old woman with a prolonged, copious alcoholic and poor food intake was hospitalized because of ascites of a few weeks' duration. Physical examination showed moderate ascites, a large liver, and a smooth, red tongue.

Needle liver biopsy revealed a histologically stationary portal cirrhosis with nodular parenchymal-cell regeneration and fibrosis, without active inflammation, fatty infiltration or cellular necrosis.

DISCUSSION

The differentiation of intrahepatic and extrahepatic biliary block in a case of icterus often poses a difficult problem for the clinician. Clinical facts and a complete set of liver-function tests may be initially inconclusive, whereupon one is faced with the choice of three alternatives: immediate exploratory laparotomy, further observation until such time as the diagnosis becomes clinically obvious and liver biopsy by the peritoneoscope or by trocar. Even under local or spinal anesthesia, abdominal exploration often produces a serious exacerbation of an intrahepatic inflammatory process and is to be avoided if possible. During the course of one or two weeks' hospitalization, clinical and laboratory findings may clearly indicate an intrahepatic or extrahepatic biliary block, but indefinite drifting without a clinical solution to the problem is undesirable. Biopsy material obtained early in the course of hospitalization will prevent uncertainty and may save time that is therapeutically valuable, as in Case 1 above.

Biopsy may also provide the only reliable information regarding the kind of intrahepatic disease present, as in Cases 2, 3 and 4. Liver-function tests and clinical data may promptly indicate intrahepatic impairment but may give only a vague idea of its nature. An exacerbation of degenerative cirrhosis with icterus is often mistaken for epidemic infectious hepatitis. Hemachromatosis without diabetes or skin pigmentation may masquerade as ordinary cirrhosis. By liver aspiration biopsy we have found other diseases clinically unsuspected, including amyloid infiltration, sarcoid, lymphoblastoma, aleukemic leukemia and carcinoma. By this method a neoplasm was obtained from deep within both enlarged hepatic lobes in 2 patients in whom peritoneoscopy had failed to demonstrate a surface lesion — Case 3 was one of these, and in the other a biopsy taken at laparotomy had also been normal. Sufficient parenchymal-cell regeneration may occur to compensate fully for a degenerative cirrhosis, so far as laboratory measures of function are concerned, even though the fibrosis present may cause serious portal hypertension. When laboratory function tests are completely normal, biopsy alone will solve the cause of hepatic enlargement.

If one is to know accurately the phase of a recognized diffuse intrahepatic disease (with the exception of simple, acute epidemic virus infectious hepatitis), liver biopsy is usually necessary. In prolonged, chronic epidemic infectious hepatitis, liver-function studies may give only a rough idea of the degree of active inflammation, cellular degeneration and fibrosis present.[10] Severe, acute "alcoholic cirrhosis" may exist without notable symptoms or marked derangement of laboratory and liver-function tests, as in Case 5. All cases of cirrhosis do not present a uniform histologic picture. Striking differences in the degree of cell necrosis, inflammatory reaction, fat vacuolization, fibrosis and liver-cell regeneration may be seen in patients with identical clinical findings and liver-function tests (Cases 6, 7 and 8). In such cases the immediate clinical response to be expected from strenuous therapy and the long-term prognosis may be indicated by the histologic state of the liver at the time treatment is instituted. Obviously, little improvement can be expected with an end-stage, stationary histologic picture, such as that in Case 8, whereas a far better prognosis is indicated by the active processes of reparative regeneration usually observed in the acute degenerative fatty livers associated with alcohol and malnutrition (Cases 5 and 7).

Liver biopsy material may provide, in addition, important indications for a specific therapeutic program. Supplements of lipotropic substances will be used with considerably more enthusiasm if appreciable fat vacuolization of the hepatic cells is observed, particularly if it is present after a pro-

longed and adequate dietary regime has been followed. Since the severity of active intrahepatic necrosis and inflammation often does not correlate with the clinical impression, as in Cases 5, 6, 7 and 8, in chronic infectious hepatitis of long duration and in degenerative cirrhosis, the obtaining of biopsy material may sometimes show the necessity for a more intensive and careful therapeutic program than would otherwise be pursued. In considering the propriety of a Blakemore surgical attack on portal hypertension by venous anastomosis in a patient with cirrhosis, a study of liver histology is desirable to rule out active intrahepatic degeneration. Its presence increases the operative risk and demands a preoperative preparation of several weeks' dietary treatment. On the basis of a diagnostic liver biopsy, specific therapy may be determined for conditions such as kala-azar, schistosomiasis, tuberculosis, syphilis, leukemia and lymphoma.

Finally, in certain types of diffuse intrahepatic disease, biopsy material is absolutely essential to accurate appraisal of the results of a therapeutic program. As a supplement to clinical and laboratory information, histologic data are particularly necessary in evaluating the various methods of treating degenerative cirrhosis and fatty liver. During the course of treatment of an acute exacerbation of cirrhosis, laboratory tests frequently give a false impression of the phase of the degenerative inflammatory process actually present, as in Case 5 above. In the face of unchanged, poor hepatic function, as measured by serial laboratory examinations, a satisfactory decision regarding when to mobilize the patient and cease heroic care may depend on biopsy findings.

In our experience, the needle aspiration biopsy method described above has been satisfactory for obtaining an optimal sampling of liver histology in patients with diffuse hepatic disease. By this procedure, trauma and maceration of the biopsy tissue have rarely been troublesome. Its very simplicity encourages its wide application as a tool for the study of abnormal physiology in disease of the human liver and as a method for making exact pathological diagnoses. To a large degree, the risk will depend on the experience and judgment of the operator and on the accuracy of the physical examination; not all patients are suitable candidates. Our mortality to date (0.5 per cent), our minimal incidence of other complications and the mortality for other published trocar liver biopsy series[5, 7] compare favorably with reported peritoneoscopic statistics[11–13] for which Benedict[11] estimates the mortality should be less than 1 per cent. It is believed that the value of the histologic information to be gained by needle aspiration biopsy more than justifies the small risk involved.

Summary

The technic and indications for use of needle aspiration liver biopsy are described.

We have performed 234 such procedures with 0.5 per cent mortality. Of the total number, 216 provided sufficient tissue for adequate histologic appraisal; in 79 cases the biopsy was essential to an accurate clinical diagnosis.

It is believed that aspiration liver biopsy will furnish the following practical information: correct differentiation of extrahepatic and intrahepatic biliary obstruction when clinical and laboratory data are inconclusive; exact diagnosis of the type of diffuse intrahepatic disease; determination of the particular phase of a known subacute or chronic hepatitis present; indications for therapy not obtainable from complete clinical and laboratory examinations; and accurate evaluation of therapeutic regimes in certain types of chronic hepatic disease.

In our experience, needle aspiration liver biopsy has proved a useful and safe measure for making exact diagnoses and for studying the abnormal physiology of liver disease.

Since this report was submitted for publication, we have attempted needle aspiration biopsies of the liver in 44 additional cases; in 43, satisfactory tissue specimens were obtained. Three further nonfatal complications were encountered: massive intra-abdominal hemorrhage requiring transfusion occurred in a patient with a normal prothrombin time (autopsy many weeks later disclosed a large subcapsular hematoma of the liver); during a transpleural biopsy approach, 15 cc. of clear bile was aspirated from a gall bladder, but no liver tissue was obtained — recurrent pain and fever during the subsequent ten days, indicating a mild right upper-quadrant bile peritonitis, subsided spontaneously; and atelectasis of the lower lobe of the right lung occurred one day after biopsy of an enlarged liver through an abdominal approach — this pulmonary collapse was presumably produced by splinting of the right leaf of the diaphragm because of severe pain following the biopsy.

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RENAL DAMAGE FOLLOWING INTRAVASCULAR HEMOLYSIS*

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BOSTON

THE sequence of hemoglobinuria followed by oliguria and anuria is well known. The observations reported below are especially concerned with the medical management of the anuric patient and with the functional and anatomic reversibility of the renal lesion produced.

In the case of anuria following massive intravascular hemolysis reported below, the patient recovered from the episode only to succumb three months later to homologous serum hepatitis. During the intervening period, the renal function showed steady improvement as evidenced by clinical and laboratory tests. Autopsy offered a unique opportunity to correlate the residual anatomic lesions with the clinical picture. In a review of the literature, no similar observation was encountered, the pathological data reported being limited to the acute phase of the condition.

Case Report

B. H., a 29-year-old housewife, was admitted to the hospital because of anuria. During the week prior to admission, an abortion had been performed at the 4th or 5th month of pregnancy, and the patient subsequently had vaginal bleeding. Three days before entry it was noted that she was pale and that the skin was "bronzed." She became weak and delirious, and was taken to another hospital, where she was unresponsive and apparently in shock. The red-cell count was recorded as 750,000, and the blood was Type A and Rh+. No difficulty was encountered in typing or cross-matching, but it was noted that the patient's blood was badly hemolyzed. A 500-cc. transfusion of Group A, Rh+ blood was given. Since the patient had not voided since admission, she was catheterized several hours after completion of the transfusion, and 30 cc. of dark-brown urine full of amorphous material was obtained. She was then transferred to the Peter Bent Brigham Hospital.

There was no history of nephritis or any indication of previous renal damage. The patient had had an earlier pregnancy, resulting in a full-term normal delivery of a healthy male infant 10 months prior to admission. There was no past or family history of anemia, jaundice or blood disorder.

Physical examination disclosed a delirious and unresponsive patient. The face was puffy, and there was a bluish-brown tint to the skin. The scleras were dull and questionably icteric. There were several hemorrhages in the fundi. The mucous membranes were exceedingly pale. Examination of the chest was negative. The heart was normal in size, and the rate rapid and regular, with occasional extrasystoles and a Grade I apical systolic murmur. The abdomen was slightly distended. The liver and spleen were not palpable. The legs showed barely perceptible edema. Neurologic examination was negative. Pelvic examination revealed a soft, boggy cervix with a widened os and some discharge from it. The uterine fundus was two or three times the normal size. There were no adnexal masses.

Examination of the blood revealed a hemoglobin of 4.4 gm., with a hematocrit of 10 per cent, and a white-cell count of 41,900, with 76 per cent neutrophils, 15 per cent young granulocytes, 4 per cent lymphocytes and 5 per cent monocytes. There were marked spherocytosis (Fig. 1) and anisocytosis and a reticulocyte count of 5.1 per cent. The fragility of the red cells to hypotonic saline solution was increased. The platelets appeared normal on smear. The serum was dark reddish brown in appearance and on the following day contained 222 mg. of hemochromogens per 100 cc., most of which was in the form of free hemoglobin (Table 1). A blood Hinton test was negative. Twenty cubic centimeters of urine obtained by catheterization was reddish brown, with a reaction of pH 7.5. The urine showed a +++ test for protein, no sugar and a positive test for bilirubin and also for hemoglobin, and the sediment contained rare red cells, many white cells and a large amount of amorphous material.

The blood urea nitrogen was 170 mg., the nonprotein nitrogen 270 mg. and total protein 6 gm. per 100 cc., with 3 gm. of albumin and 3 gm. of globulin. The fasting blood sugar was 131 mg. per 100 cc., and the carbon dioxide combining power was 15.2 and the blood chloride 110 milliequiv. per liter. No sulfonamide was detected in the blood. A stool was watery, brown and guaiac negative.

The serum was found to contain agglutinins for all Rh+ cells, and autoagglutination was observed with the patient's own cells and serum. Consequently, all transfusions given were Rh−, and there was no evidence of reaction to any of them.

During the first 6 days, the patient was given considerable quantities of whole blood, plasma, isotonic saline solution and glucose intravenously, as well as penicillin for the pelvic infection and digitalis as prophylaxis against the development of heart failure and pulmonary edema. Within 48 hours, she became more lucid, and she was rational after the 3rd day. The blood urea nitrogen continued to rise, however, and the urinary output averaged below 100 cc. daily through the 9th day. Nausea and vomiting persisted. With the development of edema and bilateral hydrothorax on the 6th day, fluids were temporarily restricted.

On the 10th day, diuresis began, with disappearance of the edema, slow decrease of the blood urea to normal and cessation of the nausea and vomiting. With the exception of an unexplained febrile period during the discontinuance of penicillin between the 23rd and 27th days, recovery was uncomplicated. The patient was discharged in good health on the 69th hospital day. The results of renal-function tests at the time of discharge and following discharge are presented in Figure 2.

The patient returned 1 month later for further studies. She had felt well in the interval. On the day prior to admission, however, slight right-upper-quadrant pain, nausea and vomiting had developed. The scleras were slightly icteric, and the serum bilirubin was elevated.

Even before this admission, several cases of jaundice had been traced to a plasma pool from which this patient had received plasma 3 months previously, and the development of hepatitis was anticipated.¶ For 4 days the patient appeared to do well, although the prothrombin time fell to 20 per cent of normal, and the serum bilirubin climbed to 13 mg. per 100 cc. On the 5th day, she rapidly lapsed into coma, dying 48 hours later of homologous serum hepatitis.

Autopsy. Post-mortem examination revealed the body of a normally developed and well nourished woman. The skin and scleras were markedly icteric. The heart and lungs were not remarkable. The liver, which weighed 1050 gm., was the usual shape but flabby in consistence, and the capsule was wrinkled; the organ was dull yellow brown. The cut surfaces varied in appearance. Large areas were uniformly pale yellow brown, and the lobular markings were indistinct. Elsewhere, the sinusoids were accentuated and bright red, and the intervening parenchyma was pale yellow and apparently decreased in amount. There was no dilatation of the

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¶The details of this icterogenic plasma pool have been reported elsewhere, and the danger of transmission of homologous serum hepatitis by the use of pooled plasma emphasized.[1]

bile passages, and examination of the gall bladder and extrahepatic bile ducts was negative.

The spleen weighed 355 gm. and was larger than normal, but was of the usual shape; it was soft in consistence. The capsule was intact and free from adhesions. Cross sections were red gray, and the malpighian corpuscles were prominent.

The right kidney weighed 140, and the left 180 gm. Both kidneys were similar and of normal shape and size. They were surrounded by a moderate amount of perirenal fat, which was not adherent to the capsule. At the hilar region, the vessels and ureters were arranged in the usual manner.

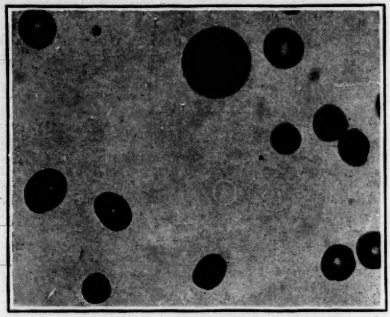

FIGURE 1. *Smear of Patient's Blood on Admission (Wright's stain).*
This shows several densely staining spherocytes.

The renal capsule was thin, gray and translucent and could be stripped from the kidney surface with ease. The capsular surfaces of the kidneys were pale brown and uniformly and firmly granular. The cut surfaces were light brown, and the demarcation between the cortex and the medulla was sharp and distinct. The width of the cortex varied between 0.6 and 0.8 cm. The cortical surfaces were mottled, and their markings were indistinct. The pyramids presented the usual appearance. The calyxes, pelves and ureters were not remarkable.

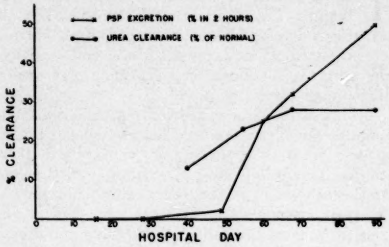

FIGURE 2. *Renal-Function Tests.*

Examination of the remaining organs revealed nothing of note.

For microscopical study, blocks of kidney tissue were fixed in Zenker's acetic acid solution and 10 per cent formalin. Sections were stained with eosin methylene blue, Mallory's phosphotungstic acid hematoxylin, Mallory's aniline blue and Turnbull's blue stain for iron.

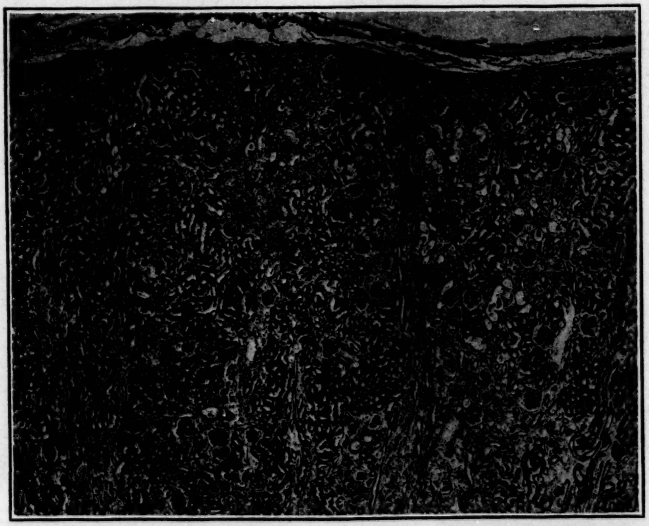

FIGURE 3. *Photomicrograph (low power) of the Kidney Cortex (phosphotungstic acid-hematoxin stain). Note the pattern of the scarring.*

The changes observed on histologic examination were definite but not extensive. There was diffuse subcapsular scarring, which frequently formed into narrow radical bands extending deep into the medulla. The fibrous tissue was occasionally pale and edematous. Throughout the scarred areas, particularly in the cortex, occasional small focal collections of lymphocytes were observed. Lymphocytes were also present in the pelvic fat and in the connective tissue beneath the pelvic epithelium (Fig. 3).

The greater number of the glomeruli were normal in appearance. The glomeruli in the scarred areas showed slight pericapsular scarring but were otherwise not remarkable.

Some of the convoluted and more particularly the collecting tubules, especially those in the outer zone, were dilated, and their lining epithelium was flattened. A few of these tubules contained pale, acidophilic-staining hyaline casts and, rarely, desquamated epithelial cells. The pattern of the involved tubules was such as to suggest the destruction of a nephron or a group of nephrons. By far the greater number of tubules showed no evidence of damage beyond slight cloudy swelling. Brown pigment granules that gave a positive reaction for iron were occasionally found in the tubular cells and throughout the stroma.

The blood vessels showed no visible involvement in either the scarred or the nonscarred areas.

Examination of sections of the liver showed massive destruction of the cells, with consequent loss of architecture. The liver cells were shrunken, with poorly stained cytoplasm and indistinct nuclear and cell outlines. There was marked polymorphonuclear infiltration about the portal areas and slight infiltration throughout the other areas. The bile ducts were intact for the most part, and in a few areas bile-duct proliferation was noted.

The sinuses of the spleen were engorged by red cells. A few macrophages contained hemosiderin. The malpighian corpuscles were enlarged but were made up of mature cells, and they were infiltrated by a few polymorphonuclear cells. There was no increase in fibrous tissue.

Sections of femoral and rib bone marrow were examined. There was marked activity in both the red-cell and the white-cell series. No abnormal forms were noted. Megakaryocytes were numerous.

Discussion

Nature of the Hemolytic Reaction

This patient developed a massive hemolytic reaction following an abortion. Although the anemia may have been due in part to bleeding, the dark urine containing blood pigments and the hemoglobinemia, abnormal fragility and spherocytosis of the red cells left no doubt that an acute hemolytic process was still in progress at the time of admission. Spherocytosis has been shown to be an indication of damage to the erythrocyte in various acute hemolytic anemias.[2] Abnormal agglutination and leukemoid white-cell reaction have also been observed in acute hemolytic anemia.[3] All these abnormalities, with the exception of the anemia, disappeared a few days after admission. The diminution of spherocytosis and fragility closely paralleled one another.

The possibility of a hemolytic transfusion reaction in the first hospital seems to be excluded by the bronze skin on admission to that hospital, the hemolyzed blood drawn for the initial matching and the fact that when the donor and recipient bloods were rechecked, both were found to be Type A and Rh+. Repeated attempts to demonstrate any subgroup Rh agglutinins* in the recipient's blood were unsuccessful. These observations indicate that the hemolytic reaction occurred before the patient received blood, presumably as a complication of the abortion.

*We are indebted to Dr. Louis K. Diamond for the Rh typing.

Drugs capable of producing hemolysis that might have been employed include the sulfonamides, quinine and abortifacient pastes. No sulfonamide was found in the blood on admission. In view of the oliguria, which would have prevented appreciable excretion of sulfonamide and thus made detection possible, sulfonamide hemolysis was not likely.

The use of quinine as an oxytocic by illegal abortionists is an old practice, and it may have been used in this case. Cases of hemoglobinuria following quinine medication in patients without malaria have been reported.[4–6] The cases reported by Wakeman et al.[5] and by Terplan and Javert[6] also occurred in pregnant women who had been given quinine as an oxytocic. The case of Wakeman and his associates was so similar to the one reported above that the following summary is presented.

TABLE 1. *Blood Data.*

Time of Determination	Spherocytes	Serum Hemochromogen	Serum Bilirubin
	per 100 red cells	*mg./100 cc.*	*mg./100 cc.*
On admission	15		2.08
After eight hours	8	222	1.48
After twenty hours	4	128	1.20
After eighty hours	2	54	0.90

A 20-year old woman took quinine and ergot to induce an abortion. Three days later she noticed severe lumbar pain and began to vomit. She became jaundiced. On admission to the hospital the urine was dark, bloody red. The serum was very dark. Attempts to group the patient's blood showed that the serum agglutinated the cells of all donors. Severe oliguria developed and the nonprotein nitrogen rose to 237. Hemoglobin, which was 73 per cent on admission, fell to 43 per cent. Diuresis began on the ninth day and the patient recovered. Re-examination of the blood later failed to show the pan-agglutination observed initially.

Severe intravascular hemolysis following the use of abortifacient pastes introduced into the uterus has been described,[7] the hemolysis being effected by the direct action of soft soaps on the red cells once they gain entrance to the blood stream.

Although the specific cause of hemolysis cannot be stated with certainty, the best explanation of the hemolytic reaction in this case seems to be either the introduction of an excess of a lytic substance into the blood stream by way of the uterus or sensitivity to orally ingested drugs.

Physiological Changes following Hemolysis

The clinical and hematologic data and fluid balance in the case reported above are presented in Table 2. The severe uremia at the onset was undoubtedly due in large part to the liberation of nitrogenous material from the metabolized red cells, as in other types of hemolytic anemia.[8]

TABLE 2. *Clinical and Hematologic Data.*

Hospital Day	Blood Urea Nitrogen	Serum Chloride	Carbon Dioxide	Albumin	Globulin	Total Protein	Phosphorus	Calcium	Hematocrit	White-Cell Count	Hemochromogens	Fluid Intake: Intravenous	Fluid Intake: Blood	Fluid Intake: Plasma	Fluid Intake: Albumin	Fluid Intake: Oral	Fluid Output: Total	Fluid Output: Urine	Fluid Output: Vomitus*	Fluid Output: Total	Weight
	mg./100 cc.	milli-equiv./liter	milli-equiv./liter	gm./100 cc.	gm./100 cc.	gm./100 cc.	mg./100 cc.	mg./100 cc.	vol. %	x 10^3	mg./100 cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	cc.	lb.
1	170	110	15.2	—	—	—	—	—	10.0	41.9	222	1,000	400	—	—	—	1,400	30	—	30	61.9
2	177	116	17.8	3.0	3.0	6.0	—	—	15.0	38.5	128	2,150	500	—	—	580	3,230	18	300	318	—
3	242	101	26.4	2.6	2.6	5.0	—	—	16.0	17.6	80	1,000	500	—	200	430	2,130	156	180	336	—
4	176	99	25.4	2.8	2.0	4.8	—	—	15.2	—	54	500	500	—	—	2,350	3,350	117	—	117	—
5	185	92	25.0	2.8	2.0	4.8	—	—	20.2	23.1	18	2,000	—	—	—	820	2,820	42	350	392	59.1
6	220	91	23.6	—	—	4.7	—	—	—	—	—	2,000	500	500	—	350	3,350	73	200	273	59.3
7	218	88	26.0	—	—	5.0	6.7	—	22.0	—	—	—	—	—	600	150	750	47	280	327	61.3
8	—	—	—	—	—	—	—	—	21.0	17.5	—	200	—	—	200	245	645	58	100	158	61.2
9	266	88	19.6	3.2	2.5	5.7	—	—	20.5	—	—	—	—	250	—	795	1,045	110	—	110	61.2
10	257	89	18.8	—	—	6.1	—	—	20.2	—	—	1,290	—	250	—	—	1,540	169	265	434	61.2
11	—	—	—	—	—	—	—	—	—	—	—	1,150	—	—	—	—	1,150	330	625	955	61.2
12	256	90	21.0	—	—	—	3.8	3.9	—	—	—	1,600	—	500	—	125	2,225	520	450	970	61.0
13	—	—	—	—	—	—	—	—	—	—	—	2,000	—	250	—	130	2,380	985	270	1,255	61.3
14	266	85	20.1	—	—	—	—	—	—	—	—	2,000	—	300	—	26	2,326	1,170	550	1,720	61.2
15	—	—	—	—	—	—	—	—	—	—	—	4,000	—	300	—	88	4,388	1,315	820	2,135	61.2
16	216	85	20.0	2.7	3.6	6.3	—	—	20.2	—	—	2,200	—	—	300	—	2,500	2,245	565	2,810	61.3
17	—	—	—	—	—	—	—	—	—	—	—	2,200	—	—	300	—	2,500	2,415	330	2,745	61.8
18	174	76	20.3	—	—	—	—	—	—	—	—	1,550	—	—	200	—	1,750	2,625	335	2,960	60.9
19	197	93	20.0	—	—	—	—	—	—	—	—	1,300	—	—	—	1,165	2,465	2,630	140	2,760	59.0
20	—	—	—	—	—	—	—	—	—	—	—	3,000	—	—	—	1,720	4,720	>1,600	210	>1,810	57.2
21	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	1,560	3,560	2,850	200	3,050	57.6
22	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1,690	1,690	2,650	—	2,650	57.6
23	131	96	18.6	—	—	—	—	—	—	—	—	2,000	—	—	—	1,875	3,875	4,310	60	4,370	54.0
24	—	—	—	—	—	—	—	—	16.0	10.2	—	2,000	—	—	—	1,915	3,915	2,610	200	2,810	53.6
25	110	102	15.6	4.2	3.0	7.2	1.9	4.2	—	—	—	—	500	—	—	1,730	2,230	2,260	180	2,440	53.8
26	—	—	—	—	—	—	—	—	18.6	11.0	—	2,000	—	—	—	1,180	3,187	2,260	300	2,560	53.4
27	—	—	—	—	—	—	—	—	—	13.7	—	2,000	—	—	—	1,810	3,810	3,000	350	3,350	53.4
28	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	1,245	3,245	1,655	100	1,755	53.0
29	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2,810	2,810	2,290	—	2,290	53.2
30	108	107	13.8	—	—	6.8	1.6	3.6	—	—	—	—	—	—	—	2,770	2,770	2,250	—	2,250	52.6
31	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,250	3,250	2,280	—	2,280	52.6
32	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,900	3,900	3,440	—	3,440	53.0
33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,110	3,110	2,950	—	2,950	52.4
34	79	109	15.6	4.2	3.3	7.5	1.3	4.8	13.5	—	—	—	500	—	—	3,250	3,750	3,190	—	3,190	52.0
35	—	—	—	—	—	—	—	—	19.8	—	—	—	—	—	—	4,210	4,210	5,100	—	5,100	52.2
36	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,410	4,410	3,390	—	3,390	—
37	81	101	12.9	—	—	—	—	—	—	6.2	—	—	—	—	—	4,200	4,200	3,130	—	3,130	51.6
38	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,050	4,050	3,390	—	3,390	—
39	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,950	3,950	3,100	—	3,100	51.0
40	63	110	—	—	—	—	—	—	—	7.6	—	1,000	—	—	—	3,850	4,850	3,150	350	3,500	—
41	—	—	—	—	—	—	—	—	—	—	—	1,000	—	—	—	3,790	4,790	3,840	—	3,840	50.7
42	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,990	3,990	3,380	—	3,380	—
43	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,550	3,550	3,800	—	3,800	50.1
44	37	105	19.0	2.9	3.0	5.9	—	—	—	—	—	—	—	—	—	3,550	3,550	2,980	—	2,980	—
45	—	—	—	—	—	—	—	—	21.5	8.2	—	—	—	—	—	4,280	4,280	3,600	—	3,600	49.9
46	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,510	4,510	3,550	—	3,550	—
47	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,900	3,900	>2,550	—	>2,550	49.2
48	38	110	17.7	—	—	—	—	—	—	—	—	1,000	—	—	—	3,340	4,340	4,350	—	4,350	—
49	—	—	—	—	—	—	—	—	—	—	—	1,000	—	—	—	3,950	3,990	4,660	—	4,660	49.6
50	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,710	3,710	3,200	—	3,200	—
51	29	105	18.4	—	—	7.2	—	—	—	—	—	1,000	—	—	—	3,900	4,900	3,660	—	3,660	49.8
52	—	—	—	—	—	—	—	—	20.0	—	—	1,200	—	—	—	3,740	4,940	4,040	—	4,040	—
53	—	—	—	—	—	—	—	—	—	—	—	1,200	—	—	—	4,200	5,400	4,140	—	4,140	50.1
54	14	111	17.9	—	—	—	—	—	—	—	—	—	—	—	—	3,240	3,240	3,500	—	3,500	—
55	15	106	—	—	—	—	—	—	—	—	—	—	—	—	—	4,050	4,050	3,150	—	3,150	49.1
56	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,610	3,610	4,200	—	4,200	—
57	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,870	3,870	2,750	—	2,750	49.8
58	17	112	20.0	—	—	—	—	—	19.0	—	—	—	—	—	—	4,910	4,910	3,350	—	3,350	—
59	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,900	4,900	4,350	—	4,350	50.6
60	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,480	3,480	2,740	—	2,740	—
61	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,000	2,300	—	2,300	50.2
62	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,000	3,330	—	3,300	—
63	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,000	2,700	—	2,700	50.0
64	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,000	2,900	—	2,900	—
65	26	109	21.6	4.2	3.2	7.4	—	—	—	—	—	—	—	—	—	3,000	3,000	2,300	—	2,300	50.4
66	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,000	2,025	—	2,025	—
67	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,450	4,450	3,350	—	3,350	51.0
68	28	107	—	—	—	—	—	—	—	—	—	—	—	—	—	5,250	5,250	3,200	—	3,200	—

*Estimated.

Oliguria, amounting almost to anuria, extended over a period of twelve days, and persistent vomiting during that period not only made feeding by mouth impossible but also caused considerable loss of electrolytes. Therapy was aimed at replacement of water, salt, plasma protein and erythrocyte deficits. Glucose and plasma served to satisfy metabolic needs in part and to prevent excessive tissue catabolism. Greater restriction of fluid was necessary at the end of the first week with the day. Pyuria also persisted until that time. The specific gravity was fixed during the first hospital admission at 1.010. On readmission a causal specimen showed a specific gravity of 1.018. These observations are all consistent with the pathological localization of the renal lesions primarily in the convoluted tubules, with subsequent repair.

It is interesting to observe that hematopoiesis was depressed during the period of convalescence so long as the blood urea nitrogen was elevated, and

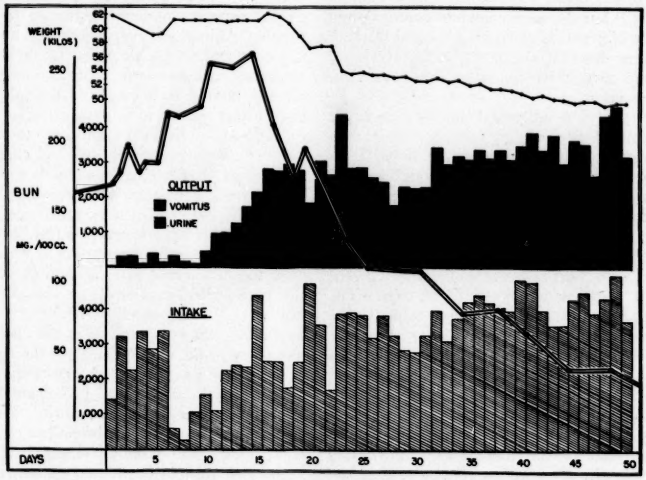

FIGURE 4. *Chart Depicting the Fluid Balance of the Patient during the Period of Anuria and Recovery.*

development of edema and hydrothorax. No determinations of serum potassium were made, but electrocardiographic changes consistent with high potassium levels[9] were not found.

With the onset of diuresis on the tenth day, the maintenance of fluid and electrolyte balance became easier. Renal function was so impaired at that time, however, that the blood urea nitrogen continued to rise (Fig. 4). Urea clearance over the following weeks improved (Fig. 2), and normal blood values were reached on the fifty-fourth day. Phenolsulfonephthalein excretion was likewise negligible at first. Inability of the tubular cells to reabsorb salt was demonstrated by a progressive fall in the blood chloride to 76 milliequiv. per liter on the eighteenth day. Subsequently, it was necessary to provide from 3 to 12 gm. of salt daily to keep the patient in salt balance. Proteinuria — as much as 8 gm. was excreted on the fifteenth day — gradually diminished, disappearing on the forty-fifth indeed for several weeks afterward. This patient was studied by the injection of radioactive iron intravenously and showed, as all uremic patients do, a decreased utilization of iron for hemoglobin formation.[10] When the azotemia had disappeared, however, active erythropoiesis was resumed, and a deficit of approximately 900 cc. of red cells was made up in a little more than a month.

HEMOGLOBINURIC NEPHROSIS

Occurrence

The majority of reported cases of hemoglobinuric nephrosis have occurred after transfusion reactions due to incompatibility between major blood groups or to Rh incompatibility.

Hemoglobinuric nephrosis also follows blackwater fever,[5, 11–13] favism,[14–17] hemolytic reactions due to sulfonamides,[18–25] plasmoquine[26] and quinine[4–6] intoxication, arsine poisoning[27] and hemolytic reac-

tions following burns[28] and the intravenous injection of distilled water.[29]

Hemoglobinuric nephrosis is rare or has not been reported in certain other hemolytic syndromes — namely, paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, cold hemoglobinuria due to a high titer of cold agglutinins and hemolysis of the recipient's cells due to a high titer of isoagglutinins in Group O blood from a universal donor.

*Renal Pathology**

The pathological changes in the kidneys following intravascular hemolysis are described by a number of authors,[30–32] but the most complete description of the sequence of events is given by Ayer and Gauld.[33] These writers describe the autopsy findings in 7 patients who died three hours to ten days after hemolytic reaction.

Three hours after hemolysis there was glomerular swelling, slight cloudy swelling of the proximal convoluted tubules and pale acidophilic material in the lumens of the proximal tubules, which became dark red to brown in the distal convoluted and collecting tubules. No interstitial edema or leukocytic infiltration was noted.

By the third day there was considerable brick-red pigment within the cells of the distal convoluted tubules and some sloughing of these cells. The glomeruli and the proximal convoluted tubules were normal in appearance. By the sixth day there was considerable interstitial edema and leukocytic infiltration around the convoluted tubules. There was marked desquamation of the tubular cells, and some of the pigment of the lumens was turning greenish yellow. By the seventh day a few mitotic figures appeared in some of the tubular cells, indicating attempts at repair. Destruction of tubular cells and interstitial infiltration and edema were still more pronounced.

By the tenth day there was complete destruction of some tubules, which were replaced by inflammatory cells and fibroblasts. There were numerous cellular casts in the distal convoluted and collecting tubules. Practically all the inflammation was around the distal convoluted tubules. There is little information available regarding what happens after the tenth day in cases that go on to recovery. Except for a case in which the patient recovered from a transfusion reaction and died fourteen months later of a pre-existing chronic glomerulonephritis, no autopsy reports of patients who had recovered from a hemoglobinuric nephrosis could be found.

The changes found in the kidneys in the case presented above were consistent with the healed stage of the pathologic sequence described. The pattern of scarring suggests that single nephrons or groups of nephrons had been destroyed. Added support to this thesis is the fact that few glomeruli and no blood vessels were involved, and none of the changes were those that are seen in the usual types of kidney disease.

Pathological descriptions of the renal lesions in other varieties of hemoglobinuria[6, 20, 34] are identical to those mentioned above after incompatible transfusion reactions.

Pathogenesis

In early pathological studies, emphasis was placed on the capacity of heme pigments to block renal tubules. Animal observations showed a much greater tendency for hemoglobin precipitation in acid urine[35]; accordingly, it was assumed that renal damage was directly related to hemoglobin precipitation, which in turn was related to urinary acidity.

There are noticeable exceptions to this explanation.[11, 33] Both experimentally and clinically, it has been noted that hemoglobinuria in the presence of an acid urine does not always result in oliguria and, conversely, that preliminary alkalinization does not always protect against severe or fatal renal damage. Fatal cases have been reported in which there has been too little renal precipitation of hemoglobin in the pathological sections[36] to account for anuria. Foy et al.,[11] in an excellent review on this subject, concluded that precipitation of hemoglobin is secondary to the oliguria and not the cause of it.

Apparently, a number of factors may operate to produce renal damage, and prominent among these is shock, regardless of the cause. Whether from hemolytic anemia, toxins, infections or trauma, the renal changes are strikingly similar.[37] The resulting tubular necrosis is considered to be due to anoxia from the critically reduced renal blood flow. The presence of hemolysis has been shown to cause further reduction of renal blood flow through local vascular spasm.[38] Finally, Yuile[39] has demonstrated quite clearly that tubular necrosis due to anoxia results in extensive hemoglobin precipitation in the tubules of experimental animals.

Dehydration and electrolyte imbalance contribute to circulatory failure. Vomiting may be severe with the sudden azotemia and, in the absence of renal regulation, may increase electrolyte loss, which in itself can perpetuate renal dysfunction.[11]

The careful observations of Bing[40] indicate a difference in toxicity of certain products of hemoglobin. Methemoglobin appeared much more toxic in acidotic dogs than bivalent hemoglobin. Formation of methemoglobin in blood serum is dependent on the length of time the hemoglobin is circulating in the serum and on the reducing capacity of the serum; in the urine, methemoglobin formation is greater in acid mediums. The possibility that other hemoglobin derivatives such as hematin cause local renal injury is suggested.

*After this article was submitted an excellent study of the pathology of hemoglobinuric nephrosis and related conditions was published by Lucké (Lucké, B. Lower nephron nephrosis: renal lesions of crush syndrome, of burns, transfusions, and other conditions affecting lower segments of nephrons. *Mil. Surgeon* **99**:371-396, 1946).

As Foy et al.[11] point out, most of the experimental studies on hemoglobinuric nephrosis have been carried out with the observer's attention concentrated on one factor. It seems fairly evident that no one factor is solely responsible for the renal change, and further studies in which each of the various factors is carefully controlled are necessary for a complete understanding of the pathogenesis.

Prognosis

The mortality rate for hemoglobinuric nephrosis cannot be accurately calculated from the published cases, since a greater proportion of fatal than nonfatal cases have undoubtedly been reported. Fifty-five fatal and 34 nonfatal cases of hemoglobinuric nephrosis collected from the literature are presented in Figure 5 according to date of death or onset of diuresis. It is apparent that the critical period following the hemolytic reaction lasts approximately two weeks. If the patient can be kept alive through that period, the kidneys may be expected to resume adequate function.

In only 7 of the 34 nonfatal cases were renal-function tests performed after clinical recovery. In all these cases function was normal, or nearly so. No case was encountered in the literature in which renal damage due to hemoglobinuria persisted for as long as a year. The results of the renal-function tests in the case reported above are shown in Figure 2. The rate of recovery was slow, but the degree of recovery was fairly complete. The final phenolsulfonephthalein determination was probably deceptively high, owing to the impairment of liver function existing at the time, but the curve shows progressive improvement until the time of death. The urea clearance apparently remained stationary at about 30 per cent between the seventieth and ninetieth days.

The prognosis of this renal lesion has much in common with other types of tubular damage, such as bichloride of mercury poisoning and shock states. Except for the initial accelerated rise of the nonprotein nitrogen with blood destruction, each case goes through the same critical period, repair proceeds at the same rate, and functional recovery is practically complete.

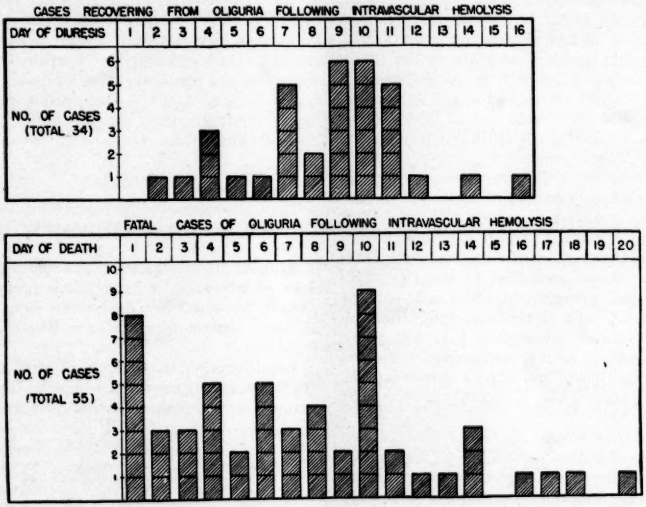
CASES RECOVERING FROM OLIGURIA FOLLOWING INTRAVASCULAR HEMOLYSIS
DAY OF DIURESIS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
NO. OF CASES (TOTAL 34)
FATAL CASES OF OLIGURIA FOLLOWING INTRAVASCULAR HEMOLYSIS
DAY OF DEATH
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
NO. OF CASES (TOTAL 55)

FIGURE 5. *Day of Diuresis or Day of Death in the Cases of Oliguria following Intravascular Hemolysis Reviewed in the Literature.*

Therapy

Treatment may be divided into the periods of hemoglobinemia, anuria and diuresis.

In the acute reaction with hemoglobinuria immediate attention should be directed to the prevention of shock and the promotion of renal blood flow. Transfusion is indicated, particularly in the presence of anemia. Plasma in amounts up to 1 or 2 liters a day or even physiologic saline and

glucose solutions are useful. Amounts of crystalloids in excess of 2 or 3 liters a day, however, are to be guarded against, because of the danger of edema if anuria develops. Immediate alkalinization is indicated in spite of the conflicting experimental evidence regarding its effects. This may be done by the injection of 6 gm. of sodium citrate, lactate or bicarbonate intravenously over a period of five or ten minutes.[41] The large doses of potassium sometimes advocated for alkalinization are not without danger,[9] particularly in view of the large amount of potassium already liberated by the hemolytic reaction.

After the first one to four days, the hemoglobinemia will have disappeared, and renal shutdown taken place. As indicated above, the lesion is reversible, given sufficient time for repair. The important factor, therefore, once anuria has set in, is time, and the maintenance of the patient depends on the prevention of edema and congestive failure, maintenance of blood volume and renal blood flow, maintenance of electrolyte balance and provision of basal nutrition requirements.

The anuric patient differs from other patients in an important respect: water and not salt is the important factor in edema formation. Without renal excretion there is a relatively fixed daily fluid output through other channels. If the fluid intake exceeds this, edema follows, regardless of the electrolyte situation. Fluid retention, in addition to causing congestive heart failure, produces functional impairment of other vital organs, particularly the brain, with cerebral edema, convulsions, coma and death. With its volume limited by a fibrous capsule, the kidney parenchyma is likewise affected by edema.

Fluids should be limited to about 1500 cc. a day, subject to modification according to the cardiac reserve and evidence of congestive failure. Blood and plasma are useful in maintaining the blood volume. Electrolyte supplements are necessary to replace those lost from the body by vomiting and diarrhea. These are prescribed according to daily determinations of the total protein, chloride and carbon dioxide combining power. Prophylactic digitalization is indicated to prevent congestive failure. Should cardiac function be impaired at the onset, it may be anticipated that the patient will not survive the critical period of one or two weeks. Under such circumstances, peritoneal irrigation may be life saving. It has been demonstrated that the peritoneal surface serves as an adequate excretory organ (by diffusion) if irrigated with the proper solution.[42] Renal decapsulation has been reported to produce dramatic results in a few cases, and it affords an opportunity for renal biopsy. It is directed, however, at prevention of the harmful effects of renal edema, which may at least in part be controlled by limited fluid administration.

Although the urine volume may become greater than normal shortly after the onset of diuresis, the nonprotein nitrogen may continue to rise. The urine at that time is almost a pure plasma filtrate — instead of the glomeruli putting out 170 liters of fluid a day and the tubules absorbing 99 per cent of the fluid, the kidney excretes 2 or 3 liters of what is approximately plasma, partially filtered of protein. This lack of tubular activity is shown as the diuresis progresses, by an inordinate loss of sodium chloride, which in itself may cause severe renal dysfunction unless corrected.[43] It is conceivable that other elements usually reabsorbed escape into the urine in excess — that is, glucose, calcium and potassium — and in themselves cause deficiency syndromes.

The period of tubular repair following the onset of diuresis may last from several weeks to several months. During this period of repair, fluids should be forced, and the intake of salt kept high (between 6 and 12 gm. daily) to compensate for the salt-losing tendency that persists until the tubular damage is repaired.

Summary

The pathogenesis of hemoglobinuric nephrosis is discussed, and suggestions regarding therapy are made.

A case of hemoglobinuric nephrosis following massive intravascular hemolysis is presented. The patient recovered but died three months later of an acute hepatic necrosis due to homologous serum hepatitis.

Renal-function tests improved until the time of death, indicating eventual complete recovery, and autopsy showed little residual kidney damage.

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GRANULOMA INGUINALE WITH PERIANAL INVOLVEMENT

Report of a Case

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GRANULOMA inguinale is an unusual skin disease found preponderantly in Negroes. The lesion begins as an ulceration in the groin or about the genitals and over a period of years, if untreated, spreads locally and progresses to a chronic inflammatory granulomatous stage. A gram-negative encapsulated bacillus appearing as a rod-like structure (Donovan body) in large mononuclear cells is the etiologic organism.[1, 2]

Involvement about the anus is rare, and yet within the past year 2 cases with perianal disease have been described in Negro soldiers stationed at a camp in Massachusetts.[3] In the ulcerative stage the chief complaints are pain and perianal drainage. The pain is constant and annoying on sitting and on walking but is agonizing on defecation, especially if the anal canal is involved. Drainage is bloody, serous or purulent, resulting in redness and irritation of the perianal skin. With progress of the disease and granuloma formation the pain tends to diminish in intensity, and the drainage becomes more profuse and foul smelling. Specific treatment consists of two courses of intramuscular antimony (Fuadin).

Inasmuch as granuloma inguinale is found primarily in warm climates and particularly in Negroes, the following case in a white man is considered worthy of report.

A 29-year-old man was seen in consultation on July 5, 1946, because of a painful, draining perianal mass of 9 months' duration. He had been born in the northeast section of Massachusetts and, except for a short period in the military service, had spent his entire life there. While in the service he had been stationed at various camps in Massachusetts, Florida and Texas. In August, 1945, he had been separated from the service because of poor vision. In September he had first noticed a small tender swelling just to the left of the anus associated with severe pain on defecation. The bowel movements at that time were scybalous, and there was occasional bright-red staining on the toilet tissue. A physician informed him that he had a "pimple" 1 cm. from the anus and prescribed a dark salve for local application and also warm-water poultices. Within a few days the mass broke down, and purulent drainage ensued. During the next few months there was intermittent crusting and recurrent drainage. The pain became intolerable and was controlled by narcotics. In April, 1946, the patient was seen by another physician, who advised admission for observation to a hospital, where physical examination disclosed a well developed and well nourished man who stood with the feet apart and who was bent forward for relief of pain. The right side of the anal canal contained a large area of ulceration, extending down to the scrotum, that bled easily after the overlying purulent discharge and debris had been removed and on which pink granulations were noted. On the left side a smaller area, about 5 cm. in diameter, was noted. The sphincter was intact and painful to examination. There was

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no evidence of hemorrhoids or fistulas. On April 29 the pathological report on a biopsy specimen taken 2 days previously revealed marked chronic inflammation and epithelial hyperplasia; early carcinoma could not be ruled out. On May 10 section of the left inguinal lymph node showed essentially normal lymphoid tissue, and the capsule disclosed slight round-cell infiltration. On May 25 biopsy of the rectum revealed marked acute and chronic inflammation compatible with lymphogranuloma inguinale. A Frei test was suggested. On May 28 it was stated that the picture was one of chronic and acute inflammation, of nonspecific type; there was no evidence of cancer. After 41 days of hospitalization, the treatment consisting of wet dressings and 6,360,000 units of penicillin, the patient was discharged unimproved, in agonizing pain — especially on defecation — and draining a profuse amount of foul pus from the perianal lesion.

The past history was entirely negative for serious sickness or operations. There was no history of contact with Negroes or of any unprotected contact.

Physical examination disclosed a young man lacking in education and of low intelligence who was poorly nourished and in obvious acute distress. Except for the perianal region,

FIGURE 1. *Photograph of the Active Lesion.*

The lesion on the anterior and left lateral aspects of the anus is ulcerated, granulomatous and covered with pink, easily bleeding granulations.

the skin was clear. The pupils reacted equally to light and to accommodation. There was no adenopathy. The heart sounds were of good quality, with normal rate and rhythm. The chest expanded symmetrically; numerous crackling rales were heard over both bases, clearing after cough. Abdominal examination was negative. There was a healed scar over the left inguinal region. The genitalia were normal. The reflexes were equal and active. About the anus anteriorly and especially on the left side there was an elliptical lesion approximately 7 cm. in length and 1 cm. in width, ulcerated anteriorly and granulomatous along the left side (Fig. 1). The mass was covered with pink granulations, which bled easily on trauma. The slightest pressure resulted in such excruciating pain that further examination was deferred. A diagnosis of probable granuloma inguinale was made, and hospitalization arranged for the following day.

The temperature was 98.6°F., the pulse 96, and the respirations 20.

Examination of the blood revealed a red-cell count of 4,910,000, with a hemoglobin of 96 per cent, and a white-cell count of 12,600, with 57 per cent neutrophils, 18 per cent band cells, 19 per cent lymphocytes and 6 per cent monocytes. The bleeding time was 3 minutes (Duke), and the clotting time 5 minutes (capillary tube), and the sedimentation rate 10 mm. in 1 hour (Wintrobe method). The Frei test and the blood Hinton test were negative 72 hours after admission. The urine was straw colored, cloudy and alkaline, with a specific gravity of 1.016; tests for albumin and sugar were

FIGURE 2. *Photomicrograph of the Biopsy Specimen (x100). Note the marked chronic inflammation in the subpapillary connective tissue.*

negative. Microscopical examination of the sediment was negative for red cells and casts.

Strict bed rest was enforced and Furacin-ointment dressings applied to the perianal region; 0.06 gm. of codeine sulfate

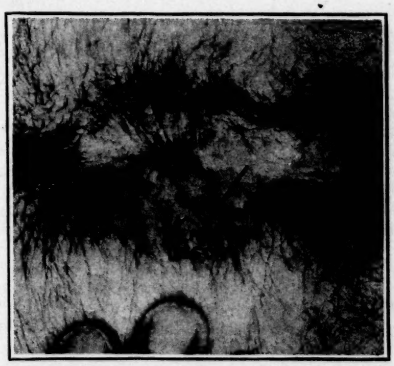

FIGURE 3. *Photograph of the Healed Lesion.*

The perianal lesion is healed after fourteen days of specific treatment.

and 0.6 gm. of aspirin were administered for relief of the pain. Intragluteal injections of Fuadin (sodium antimony-III biscatechol disulfonate of sodium) were instituted on the day of admission, alternating buttocks being used, and a complete course (40 cc.) given according to the following schedule: on

July 6, 7, 8 and 10, respectively, 1.5, 3.0, 5.0 and 5.0 cc., followed by 5.0 cc. every other day until the full amount had been given. Biopsy specimens and smears were taken from the perianal lesion on July 9. The smear was negative for acid-fast bacilli and for inclusion bodies. Microscopical examination of one biopsy specimen revealed a thickening of the epidermis, with edema, polymorphonuclear-cell and lymphoid-cell infiltration of the papillae and a dense lymphoid and plasma-cell exudate in the subpapillary connective tissue. There was no evidence of tuberculosis, and the inflammatory process was considered nonspecific. The diagnosis was chronic and acute inflammation. Microscopical examination of the other specimen disclosed marked chronic inflammation and epithelial hyperplasia compatible with granuloma inguinale (Fig. 2).

On the 4th hospital day there was little drainage, and the pain had diminished noticeably. At that time the ulcerated portion of the lesion showed evidence of crusting and drying, and there was a definite decrease in redness about the entire area. Clinical improvement was marked, and the patient was allowed out of bed. During the following week the ulceration gradually healed, and the granuloma was absorbed. All symptoms subsided. The first course of treatment was completed on July 20, and 2 days later the patient was discharged to his own physician for the second course, with the lesion apparently healed (Fig. 3). Despite the fact that this course was never completed, owing to indifference on the part of the patient, there has as yet been no recurrence.

Several aspects of this case are worthy of consideration. The diagnosis of granuloma inguinale is extremely difficult, not only because the lesion is not suspected but also because smears and biopsy specimens often do not reveal the diagnostic bacteriologic and pathological findings. The disease should be suspected in every ulceration or granuloma of the anogenital region that is resistant to antibiotics and to chemotherapy. Even though the characteristic macrophage with intracellular Donovan bodies is not found on smear examination and the pathological picture is that of acute or chronic inflammation or of nonspecific granuloma, a therapeutic trial of intramuscular antimony (Fuadin) should be instituted.

Granuloma inguinale can become a chronic disabling disease, if not recognized. Clinical response to Fuadin is usually prompt, dramatic and specific. The case reported is of interest in that it occurred about the anus and in a white man living in Massachusetts.

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MEDICAL PROGRESS

"FOLIC ACID": PTEROYLGLUTAMIC ACID AND RELATED SUBSTANCES*

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CHICAGO

THE discovery, isolation, synthesis and clinical use of a new member of the vitamin B complex called "pteroylglutamic acid" can be attributed to the combined efforts of many different investigative groups. During the past sixteen years this substance has ascended from bacteria to chick, from chick to rat, from rat to monkey and from monkey to man as an essential nutrient. During its ascent, but before its isolation and synthesis, this substance picked up many names (Table 1), for each group of investigators that studied it did not then realize that their material was quite similar to that described by others. This varied nomenclature was the natural consequence of preliminary work on an unknown substance, but the identity of this nutritive essential was clarified when it was shown that the factor in liver essential for the growth of *Lactobacillus casei* was also necessary for chicks, rats, monkeys and man.

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Discovery, Synthesis and Chemistry

Various investigative groups have demonstrated that in such foods as yeast, liver and spinach, there is a substance or group of substances that is closely associated with known members of the vitamin B complex and is necessary for the growth and hematopoiesis in the chick, the rat and the monkey, as well as for the growth of certain bacteria. Investigators working chiefly with yeast isolated a material known as the *L. casei* factor because it was necessary for the growth of that organism.[2-4] From liver a substance was isolated that prevented the development of anemia, leukopenia and thrombocytopenia and restored growth in the chick.[2-4] This substance was called vitamin B_c. From both liver and yeast a factor was isolated that prevented the development of cytopenia and a sprue-like syndrome in monkeys fed a synthetic diet containing all previously known essential nutrients.[2-4] This factor was named vitamin M. As knowledge of these apparently different factors accumulated, it occurred

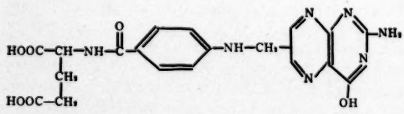
to various investigators that they might be dealing with the same substance. It was rapidly shown that the *L. casei* factor could replace vitamin B_c in chick nutrition and could correct the sprue-like syndrome in monkeys deficient in vitamin M.[2-4] Furthermore, it was found that the *L. casei* factor corrected the anemia, leukopenia and granulocytopenia and restored growth to rats fed sulfonamides.[2-5] When it had been demonstrated that these various factors

TABLE 1. *Early Names Applied to "Folic Acid"* by Various Groups of Investigators.*

SUBJECT OR BIOLOGIC ACTIVITY	NAME
Bacteria	
Lactobacillus casei	*L. casei* factor; norite eluate factor; yeast factor; fermentation factor.
Streptococcus lactis R. (*Str. faecalis*)	*S. lactis R* factor; folic acid.*
Chick	Vitamin Bc; vitamin Bc conjugate; vitamin B_{11}; vitamin B_{11}; factor U; factor R; factor S.
Monkey	Vitamin M
Man	Wills factor (?)

*Folic acid was the name given by Mitchell and his associates[1] to a factor extracted from spinach, essential for the growth of *S. lactis R.* This substance is not identical with the *L. casei* factor but has been extracted from liver, kidney, yeast and mushrooms. "Folic acid" has come into popular usage as the descriptive term for pteroylglutamic acid and its related substances. Throughout this paper these substances are designated by their accepted chemical names when the names are known.

were probably closely related, if not identical, the *L. casei* factor was crystallized from a liver concentrate, its chemical structure determined, and its synthesis achieved.[2-4, 6] The active nutrient thus isolated proved to be a relatively simple organic compound containing the amino acid, glutamic acid, para-aminobenzoic acid and the pterin nucleus related to xanthopterin, the chemical that gives the yellow color to the butterfly wings. These various fractions of the active material are combined as follows:



This compound is called pteroylglutamic acid. It is the active substance in the preparations formerly called vitamin B_c, vitamin M and *L. casei* factor. "Folic acid" is the term that, by popular usage, has become synonymous with pteroylglutamic acid, but throughout this review the latter chemical name is used. Pteroylglutamic acid is a bright-yellow material that is only slightly soluble in water. Its sodium salt is more soluble. Sunlight has a destructive action on a solution of pteroylglutamic acid, and this compound is rapidly destroyed by heating with dilute mineral acids.[7]

A series of compounds containing more than one glutamic acid molecule has been isolated from various sources. The active material in the preparation containing the so-called "fermentation *L. casei* factor" has recently been identified and synthesized. This factor occurs in a concentrate of the filtrate obtained from the products of aerobic fermentation of an unidentified bacterium of the genus *Corynebacterium*.[8] The active material possesses two extra glutamic acid molecules bound through a peptide linkage to pteroylglutamic acid. This compound is known as pteroyltriglutamic acid (or pteroyldiglutamyl-glutamic acid). A different chemical was isolated from a yeast concentrate. This compound, formerly known as vitamin B_c conjugate, proved to have six molecules of glutamic acid combined — probably through a peptide linkage — to pteroylglutamic acid. Hence, it was named pteroylheptaglutamic acid (or pteroyl-hexaglutamyl-glutamic acid). The exact structure of this compound is not known, for it has not been synthesized. In the literature pteroylheptaglutamic acid is frequently referred to as "folic acid conjugate." Recently, a compound containing thirteen glutamic acid molecules has been isolated from yeast.[9] The exact chemical structure has not been determined. On the basis of these chemical studies it seems reasonable to infer, as Thomson[9] has implied, that a whole series of compounds that might collectively be called the pteroylpolyglutamic acids exists in nature.

Pteroic acid is a synthetic compound containing no glutamic acid molecules.[6] This compound has relatively limited biologic activity.

ASSAY AND NATURAL DISTRIBUTION

The amount of pteroylglutamic acid or its related conjugates in foods and biologic fluids can now be determined only by bioassay, the growth of *L. casei* or *S. lactis R* being used as the test organisms. The amount of growth of these bacteria in a given time is estimated turbidimetrically. From a standard curve the concentration of active material in the unknown substance can be estimated. This assay, to be accurate, depends on knowledge of the nutritional requirements of these test organisms. Table 2 presents the relative biologic activity of pteroylglutamic acid and related substances for *S. lactic R* and *L. casei*. Two points should be emphasized: the nutritional requirements of the test bacteria are different regarding their need for these growth-promoting factors and compounds containing more than one glutamic acid molecule are less active than pteroylglutamic acid in promoting growth.

It is the second point that is especially important in the assay of pteroylglutamic acid in foods, for in nature this nutrient almost uniformly occurs as pteroylheptaglutamic acid.[10] Because this heptapeptide is relatively impotent as a growth-promoting factor, the compound must be hydrolyzed into simple

pteroylglutamic acid, which is a potent growth factor. This hydrolysis may be achieved in a number of ways. Some investigators employ the enzyme takadiastase; other workers use an alkaline or acid hydrolysis. In animal tissues an enzyme has been found that hydrolyzes pteroylheptaglutamic acid into pteroylglutamic acid and six molecules of glutamic acid.[11, 12] This enzyme is designated vitamin B_c conjugase because it splits the heptapeptide vitamin B_c conjugate (pteroylheptaglutamic acid). Vitamin B_c conjugase has been found in relatively abundant amounts in the liver, kidneys, bone marrow and pancreas. In the microbiologic assay for pteroylglutamic acid a water extract of fresh hog kidney is used as a source of vitamin B_c conjugase.[10] There is, however, a limitation to this method — namely, the occurrence in food of a substance called "conjugase inhibitor."[10] Because this factor, which inhibits the activity of vitamin B_c conjugase, occurs in variable amounts in food and because there is at present no way of destroying it, assays employing vitamin B_c conjugase are necessarily of limited value. By the use of amounts of conjugase in excess of the inhibitor content of the particular preparation being assayed, this difficulty may in part be overcome. No matter which hydrolytic method is employed, however, the amount of pteroylglutamic acid found in various foods varies rather widely, and to date a completely satisfactory method of assay has not been worked out.

Table 2. *Relative Biologic Activity of Pteroylglutamic Acid and Related Substances.*[7]

Substance	Activity	
	S. lactis R.	*L. casei*
Pteroic acid	50.0	0.01
Pteroylglutamic acid	100.0	100.0
Pteroyltriglutamic acid	7.5	80.0
Pteroylheptaglutamic acid	0.3	0.2

With these limitations in mind, some of the recent work on the concentration of pteroylglutamic acid in foods is presented in Table 3. A number of points should be emphasized. In the first place, even in foods containing relatively rich quantities of pteroylglutamic acid, the amount available is low. In the second place, cooking and storage at room temperature effect large losses of this nutrient.[10, 13] Finally, only small amounts of pteroylglutamic acid are present in the usual diet — amounts considerably less than that found therapeutically effective. The intestinal bacterial flora may contribute a large amount of this vitamin, for Williams and his associates[14] have shown that a wide variety of bacteria can synthesize folic acid and that the rat may obtain as much as 70 per cent of the daily intake of folic acid from bacterial activity. Biosynthesis of pteroylglutamic acid in human beings has not been studied. Furthermore, the optimal daily allowance of this nutrient for human beings has not been determined.

Physiology

The reported signs of pteroylglutamic acid deficiency are summarized in Table 4. It is apparent that a wide variety of signs are associated with a deficiency of this substance. Of special interest, however, are the hematopoietic disturbances in various animals and the syndrome similar to cytopenia and sprue that occurs in monkeys. The hematopoietic disturbances — anemia, leukopenia, granulocytopenia and thrombocytopenia — that occur in the lower animals do so in animals maintained on a synthetic diet containing all the known nutrients except pteroylglutamic acid. This factor specifically corrects all these disturbances when added to the purified diet.[2, 15]

Table 3. *Content of Pteroylglutamic Acid in Various Foods.*[10,13]

Food	Pteroylglutamic Acid Content
	microgm./100 gm.
Fresh deep green leafy vegetables	80–190
Liver	48–105
Fresh green vegetables; cauliflower.	40–62
Kidney	35–47
Dry breakfast cereal prepared from wheat	19–46
Beef; veal.	11–22
Root vegetables, tomatoes, cucumbers, light green leafy vegetables, bananas, pork, ham, lamb, cheese, milk, dry breakfast cereal prepared from rice or corn and many canned foods	0–20

Table 4. *Reported Signs of Pteroylglutamic Acid Deficiency.**

Deficiency Sign	Test Subject
Failure of growth	Chick, rat, guinea pig, mouse and monkey
Anemia	Chick, rat, monkey and man
Leukopenia	Rat, chick, monkey and man
Granulocytopenia	Rat, monkey and man
Thrombocytopenia	Chick and man
Poor feathering	Chick
Diarrhea	Monkey and man
Gingivitis	Monkey
Necrosis of gums	Monkey
Susceptibility to dysentery	Monkey
Achromotrichia	Rat and chick
Porphyrin-caked whiskers	Rat
Subnormal hepatic level of pantothenic acid	Rat
Subnormal response to stilbestrol	Chick
Subnormal response to niacin	Dog
Spastic type of cervical paralysis	Turkey poult
Certain dermatologic syndromes	Man
Perosis	Chick

*Based on material presented by Daft.[15]

In the syndrome similar to cytopenia and sprue that develops when monkeys are maintained on a purified diet, interest is great because of the homologous conditions in man — tropical and nontropical sprue and celiac disease. In fact, Jones, Warden and Darby[16] suggest that lack of vitamin M in the monkey is the experimental analogue of sprue in man. This deficiency syndrome in the monkey

consists of anemia, leukopenia, thrombocytopenia, gingivitis, necrosis of the gums, anorexia, diarrhea, susceptibility to dysentery (experimental or spontaneous infection) and finally death.[17, 18] This syndrome, as well as sprue in man, responds to therapy with both pteroylglutamic acid and pteroyltriglutamic acid. In addition to the steatorrheic diarrhea of man, certain cases of long-standing diarrhea among human beings have responded to treatment with pteroylglutamic acid.[19] Coca[20] reported that 6 patients with the dermatologic syndrome, who presented symptoms and signs that did not respond to routine therapy for allergy, were successfully treated with pteroylglutamic acid. These patients had nervous symptoms or dermatologic disturbances, or both. The former included "anorexia, weakness, uncontrollable nervousness and insomnia," and the latter either "chronic early inflammatory eruptions of both legs" or "widespread weeping eruption of limbs, body and face."

Because there is little fundamental knowledge concerning the mode of action of pteroylglutamic acid, few broad hypotheses have been suggested. Two theories should be mentioned. On the one hand it has been suggested that pteroylglutamic acid acts as a co-enzyme in the synthesis of thymine (5-methyl uracil — a pyrimidine not to be confused with thiamine) or a related compound.[15] The evidence for this mode of action, however, is far from convincing. By analogy, it is reasonable to suspect a similar action with all the other known members of the vitamin B complex, which have been shown to act as co-enzymes in bodily metabolic processes. Spies and his associates[21–23] have shown, in a small series of cases, that 5-methyl uracil in large amounts can be substituted for pteroylglutamic acid in the treatment of macrocytic anemias. Petering and Delor[24] have demonstrated that 5-methyl uracil will not restore growth or correct the hematologic disturbances in rats deficient in pteroylglutamic acid. The explanation may be that a large number of natural and synthetic hematopoietically active substances exist. Such substances may be related chemically, and their mode of action may be similar.[3] On the other hand, it has been suggested that pteroylglutamic acid plays a role in nitrogen metabolism, for in rats casein affects a partial protective action against the production, by various sulfonamides, of signs of nutritional deficiency.[5, 15]

These hypotheses leave much room for fundamental research, but there is more knowledge regarding the action of these hematopoietic substances in Addisonian pernicious anemia. In studying this disease investigators have employed two methods of assessing the activity of pteroylglutamic acid and its related substances: the hematologic response, including cytologic changes in the bone marrow, and the urinary excretion of pteroylglutamic acid following oral or parenteral administration of this substance or its relatives.

In patients with pernicious anemia in relapse a satisfactory remission can usually be produced with pteroylglutamic acid. The hematopoietic response to the heptapeptide, pteroylheptaglutamic acid, depends on the amount of conjugase inhibitor in the preparation. If the inhibitor content is high, there will be no change in the blood picture. If, on the other hand, the inhibitor content is low, there may be a hematologic remission.[25] These data suggest that the patient with pernicious anemia cannot utilize the heptapeptide owing to an inability to neutralize the activity of conjugase inhibitor. In cases undergoing remission, there is a reticulocytosis followed by a gradual increase in the red-cell count and hemoglobin, together with a conversion of the characteristic maturation arrest of bone marrow into a normal cytologic picture.[2, 3, 11, 12, 25–31]

What changes occur in urinary excretion of pteroylglutamic acid? Studies of this problem by Bethell and his associates[25, 32] are the most complete to date. The investigators divided the subjects into three groups: normal subjects, patients with pernicious anemia in relapse and patients with pernicious anemia in remission on liver. Each of these groups was studied while the subjects were on a standard low-protein, meat-free diet of adequate caloric value, while the standard diet was supplemented with pteroylglutamic acid and while the standard diet was supplemented with yeast containing an equivalent amount of pteroylheptaglutamic acid. In the last, a variety of preparations containing different amounts of conjugase inhibitor were tested. In no case was any heptapeptide found in the urine. Three significant observations were made. In the first place the normal person excretes equal amounts of pteroylglutamic acid whether the diet is supplemented with pteroylglutamic acid or purified heptapeptide. When, however, a preparation of heptapeptide containing a large amount of inhibitor is used as the supplement, the excretion of pteroylglutamic acid is reduced. Secondly, the patient with pernicious anemia in relapse excretes much less pteroylglutamic acid than the normal subject when the diet is supplemented with either pteroylglutamic acid or purified heptapeptide. If such a patient is given a heptapeptide preparation that is rich in inhibitor, there is practically no increase in the urinary excretion of pteroylglutamic acid over that occurring while he is on the standard diet. When given liver extract along with heptapeptide high in conjugase inhibitor, the patient with pernicious anemia in relapse will show no increase in urinary excretion of pteroylglutamic acid. Finally, the patient with pernicious anemia in remission on liver excretes about the same amount of pteroylglutamic acid while receiving this supplement as the normal subject does. When given the heptapeptide in addition to conjugase inhibitor, he is able

to excrete much more pteroylglutamic acid than the patient in relapse.

Thus, the combination of liver extract and heptapeptide given to the patient with pernicious anemia in relapse does not cause an increased urinary excretion of pteroylglutamic acid. In a few patients with pernicious anemia in relapse receiving no supplement of heptapeptide, parenteral liver extract alone seems to cause a small but definite increase in the urinary excretion of pteroylglutamic acid.[33] This report has not yet been confirmed.

How are these preliminary metabolic studies to be interpreted? It appears that patients with pernicious anemia in relapse are unable to utilize pteroylheptaglutamic acid because they are unable to neutralize the inhibitor. In contrast, patients in remission show marked improvement in their handling of heptapeptide. These observations are of interest, for studies in vitro have shown that the conjugase activity in tissues from patients with pernicious anemia is not significantly different from that of normal subjects.[11, 12] On the basis of the evidence so far available two interpretations have been offered. It has been suggested, on the one hand, that purified liver extracts contain substances that correct some abnormality in the conjugase enzyme system in patients with macrocytic anemias. The mechanism may be the removal of an inhibitor substance of conjugase or the providing of substances necessary for proper functioning of this enzyme system. Secondly, the metabolic derangement may be more deeply seated than mere inability to utilize the heptapeptide of pteroylglutamic acid.[34] Of great interest in connection with the interrelations between pteroylglutamic acid and liver extract is the recent experiment of Elvehjem and his co-workers,[35] who found that niacin-deficient dogs developed an anemia that ultimately failed to respond to niacin. No response to folic acid was noted, and refined liver extracts were effective only when the diets were high in casein or when supplements of pteroylglutamic acid were given. This point is more fully explained below.

Pharmacology and Toxicology

Both in animals and in man pteroylglutamic acid and its relatives are nontoxic.[36] In animals these substances are not irritating when injected subcutaneously. They do not affect the blood sugar, and there is only a weak action on the isolated intestine. Respiration is not influenced, and the effects on the blood pressure are minor. In long-term experiments, the daily intraperitoneal administration of 5 mg. per kilogram of body weight for two months produced no unfavorable reactions in rabbits and rats. In a similar period, daily peritoneal injections of 50 mg. per kilogram of body weight to rabbits and 75 mg. per kilogram of body weight to rats caused minor changes in the kidney tubules but no deaths. The acute toxicity for experimental animals is low. The LD_{50}* for mice is 600, for rats, 500, for rabbits, 410 and for guinea pigs, 120 mg. per kilogram of body weight.

In human subjects oral or intramuscular administration is essentially without toxic effects. Up to 150 mg. has been given intramuscularly, and 500 mg. orally in a single dose. Intravenous medication, on the other hand, is not recommended, for in a few cases rapid intravenous administration of 150 mg. of pteroylglutamic acid has resulted in a shock-like reaction. The pulse has disappeared, the blood pressure has fallen, and unconsciousness has ensued. Fortunately, recovery has always followed within several minutes, although headache and nausea have persisted for as long as twenty-four hours. This shock-like reaction may, however, be due to impurities in the synthetic preparations.[11]

The therapeutic dosage currently recommended by most authors is 10 mg. daily by mouth.[27, 37, 38] For maintenance, 5 to 10 mg. usually suffices. In any case these doses may be varied depending on the individual case. Davidson and Girdwood[27] suggest that if clinical and hematologic responses do not occur within two weeks, it can be assumed that the disease being treated is not due to a deficiency of pteroylglutamic acid and that continued administration of the vitamin is contraindicated.

*LD_{50} represents the amount of pteroylglutamic acid (mg. per kilogram of body weight) that will kill 50 per cent of the animals within the test period.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33441

PRESENTATION OF CASE

First admission. A fifty-nine-year-old married Italian laborer was admitted to the hospital because of back pain.

Five months before admission the patient was first seen in the Out Patient Department because of pain in the left sacroiliac region, which had begun two and a half months previously while he was shoveling in a gravel pit. He admitted that similar brief attacks had occurred for about six months, but these had always cleared spontaneously. For the past two and a half months, however, the pain persisted despite strapping, heat, massage and rest. He also complained at bedtime of intermittent attacks of numbness over the outer aspect of the left thigh and an occasional sharp shooting pain from the left sacroiliac joint to the knee over the outer aspect of the thigh. He walked with a limp, used a cane and could produce only slight movement of the lumbar spine. An x-ray film at that time revealed moderate degenerative hypertrophic changes. There was no destructive or developmental abnormality. Conservative therapy was of no avail. The spinal fluid and a myelogram one month before entry failed to show any abnormalities. The patient continued to complain of the same difficulties and had lost 30 pounds of weight. During the week before entry a small nodule, 1.5 by 2.5 cm., appeared in the region of the upper third of the left sacroiliac joint and was firm and tender and caused reproduction of the referred pain and numbness along the anterolateral aspect of the left thigh.

Physical examination revealed that bending in any direction caused pain. Straight-leg raising was possible from 38 to 50° with tight hamstrings. Coughing and sneezing caused no pain. The reflexes were equal and hypoactive bilaterally in the legs. There was local tenderness over the lumbar and left sacroiliac regions. Recent weight loss was evident. The scleras were slightly icteric. There was deep tenderness in the right upper quadrant, with a palpable liver edge 2 cm. below the costal margin on deep inspiration and the upper edge percussed at the top of the sixth rib. A questionable, deep, irregular, poorly defined mass was noted in the right upper quadrant and right paraumbilical region. The spleen was questionably palpable.

The blood pressure was 160 systolic, 95 diastolic.

Examination of the blood showed a red-cell count of 4,870,000, with 85 per cent hemoglobin, and a white-cell count of 8400, with 62 per cent neutrophils. The urine was normal.

Liver-function tests were negative except for a ++++ cephalin-flocculation test in twenty-four and forty-eight hours and a van den Bergh reaction of 1.2 mg. per 100 cc. direct and 2.3 mg. indirect. A plain film of the abdomen revealed a liver somewhat smaller than that usually expected and a spleen within normal limits. A gastrointestinal series was normal. Barium enemas were not totally satisfactory because of pectenosis, but no definite abnormality was seen. Three weeks after admission the van den Bergh reaction fell to 0.5 mg. per 100 cc. direct and 0.9 mg. indirect. A cephalin-flocculation test was ++ in twenty-four hours and +++ in forty-eight hours. An intravenous pyelogram revealed normal kidneys, but the third lumbar vertebra at its left lateral aspect showed a loss of normal outline, with an irregular, moth-eaten appearance at this portion of the body, and the left transverse process suggested destruction. Also, there was loss of the articular facet on the left. The left psoas shadow appeared to bulge slightly opposite the lesion. No other destructive areas were seen. Alkaline and acid phosphatase levels were normal. An aspiration biopsy of the lumbar vertebra revealed a malignant tumor, unclassified, with a question of liposarcoma. X-ray therapy was instituted for relief of the pain with good success and some sclerosis of the lumbar vertebra. The patient was discharged two months after admission.

Final admission (two years later). He was seen in the Out Patient Department ten months after discharge, when there appeared to be no progression of the destruction of the left third lumbar vertebra but rather some evidence of further recalcification. A month later, however, the jaundice, which had disappeared for a while, recurred and began to increase. The patient developed lower abdominal pain, and his appetite became poor.

It was discovered on this admission that in his early youth he had been a heavy drinker, averaging 12 to 18 bottles of beer daily, with occasional wine or whisky for many years and irregular eating habits at that time. About thirty years previously he had had an attack of fairly marked jaundice with itching, which had subsided completely on medical treatment. Since then he had had occasional bouts of dark urine, and he believed that his eyes may have been yellow from time to time.

Physical examination disclosed an intensely icteric man with a smooth fine skin, rather sparse hair and scattered spider telangiectases over the

chest and back. The liver edge was palpable 7 cm. below the costal margin. There was no evidence of ascites. The liver was questionably slightly nodular. There was slight tenderness over the lumbosacral joint.

The blood pressure was 134 systolic, 78 diastolic.

Examination of the blood revealed a red-cell count of 4,830,000, with 10.5 gm. of hemoglobin, and a white-cell count of 4600, with 86 per cent neutrophils. The urine gave a + test for albumin, and the sediment contained cellular casts. The alkaline phosphatase was 13.7 units per 100 cc. The bromsulfalein test disclosed 100 per cent retention of the dye. The total protein was 7.68 gm. per 100 cc., with 3.88 gm. of albumin and 3.80 gm. of globulin; the nonprotein nitrogen was 28 mg., and the fasting blood sugar 158 mg. per 100 cc. A cephalin-flocculation test was ++++ in both twenty-four and forty-eight hours. The prothrombin time was 42 seconds (control, 15 seconds). The acid phosphatase was 1.5 units per 100 cc.

An x-ray film of the chest revealed evidence of old pleurisy at the left costophrenic angle and an area of increased density, 3 mm. in size, in the left third interspace that might have been a blood vessel but could have been a small metastatic nodule. Marked arthritic changes were noted in the dorsal spine; a defect in the body of the third lumbar segment remained unchanged, and a soft-tissue mass still distorted the left psoas muscle. There seemed to be a mass in the epigastrium, which might have been the liver. In the hospital the prothrombin time rose, the patient developed guaiac-positive stools, and the nose began oozing blood. He developed complete anorexia to the point of nausea and had severe lower abdominal pain. He became anuric, and on the fifth hospital day the prothrombin time was 84 seconds against a 15-second control. On the sixth hospital day he developed a strong cholemic odor, became totally unresponsive and died.

Differential Diagnosis

Dr. William Clark: It is quite apparent that this patient had severe liver disease and that involvement of that organ had been present, at least in recurrent form, for a thirty-year span. The terminal illness was one of liver failure, with associated renal involvement. In addition there was an episode of back pain, which was explained by the finding of a neoplasm involving the lumbar spine, two years before the final admission.

May we see the x-ray films?

Dr. Milford D. Schulz: The only available films of the spine are those made after x-ray therapy, so that I cannot say how the bones looked before treatment. The sclerosis that can be seen is probably the result of treatment. I can only point out the area of destruction in the third lumbar segment involving the small parts of the vertebra as well as its body. The soft tissue in the left psoas region bulges and displaces the ureter. I do not know whether the shadow described in the lung represents a metastatic nodule or not. The only other thing that might be mentioned is the fact that these films of the esophagus are not adequate to allow one to say that the patient did not have varices. Nor does there seem to be a mass extending through the diaphragm from the liver.

Dr. Clark: We do not have the necessary films to help us determine the size of the liver or whether the mass was part of the liver. I should like to ask about the tumor. It is too bad that we do not have the older films. Are you reasonably certain that the tumor arose in the lumbar vertebras and extended into the psoas region, or is it possible that it invaded the vertebras from without?

Dr. Schulz: I think that the latter is a possibility, but something arising in the vertebral body seems likelier. The whole affair could be a metastatic tumor.

Dr. Clark: Do you think that it is unusual for metastatic tumors of the lumbar spine to break through and invade into the soft tissue?

Dr. Schulz: It is rare, but not impossible.

Dr. Clark: Primary tumors of the lumbar spine are not common. Most of the tumors of this area are metastatic lesions. I think we can safely assume that the predominant symptomatology at the first admission can be explained by the neoplasm. The pathological report of the nature of the neoplasm is difficult to evaluate. The tumor could not be definitely classified, as the pathologist stated, and I assume that it had many of the characteristics of a liposarcoma — a diagnosis that in itself, as I understand it, is usually made with some hesitation. At least in a case reported here in 1942,* Dr. Mallory offered some apologies when he made the diagnosis of liposarcoma. Liposarcomas are reported to be radiosensitive, and I assume that there is good x-ray evidence that this tumor was radiosensitive. In addition, the symptoms improved. There is very little more that I can say about the diagnosis other than to accept it. The diagnosis is a reasonable explanation for the back pain. It is interesting that among the liposarcomas that are described, some start in a bone and invade the soft tissue and have been mistaken for soft-tissue tumors at operation. They are also said to be encapsulated. The problem is how to evaluate the tumor in relation to the liver disease.

The presence of both severe liver disease and a malignant tumor makes one want to conclude that this patient had a tumor in the liver, with metastases to the spine, or tumor of the spine metastasizing to or encroaching on the liver tissue and producing liver failure. I can find nothing in the protocol that will support either hypothesis, and I shall

*Case records of the Massachusetts General Hospital (Case 28052). *New Eng. J. Med.* 226:204, 1942.

consider two separate diseases. The patient had had liver disease at twenty-nine years of age. I prefer to postulate two separate entities rather than two different types of liver disease. I shall try to develop the hypothesis that he had cirrhosis; that will make it easy to assume that the tumor did not metastasize to the liver, because we know that such metastasis does not usually take place.

In looking back through the record we have to deal with seemingly repeated episodes of jaundice, although we have only one clear-cut story. The history is also complicated by the fact that the patient consumed a large amount of alcohol. We do not associate alcohol consumption with acute episodes of hepatitis accompanied by jaundice, but rather with insidious changes characterized by fat being deposited in the liver that in some manner is related to nutrition. The best conclusion that we can draw regarding the episode of jaundice at the age of twenty-nine is that he had hepatitis of a cholangitic type as evidenced by the itching. Then we are told that following this he had episodes in which the urine was dark and that he probably had jaundice. I assume that these episodes were recurrences of the phenomenon that appeared at the age of twenty-nine.

He had jaundice at the time of the first admission to the hospital and at that time the liver was palpable but was not considered to be enlarged by the radiologist. Although one can conclude that he had some form of active liver disease, the tests performed at that time and the physical findings do not lead one to make a diagnosis of cirrhosis. After a remission of symptoms and physical signs he again exhibited signs of severe liver damage at the time of the final admission, and telangiectases or spider nevi were also found. The liver was described as enlarged and somewhat nodular, and I shall conclude that if nodules could be felt the liver was likewise firm. Even on the last admission, careful analysis revealed very little with which to make a diagnosis of cirrhosis of the liver. Perhaps the physical findings were the only things that definitely lead in that direction. The liver tests showed severe liver damage, but I do not believe that the tests in themselves imply cirrhosis. The repeated episodes of hepatitis with jaundice, which I believe to have been associated with cholangiolitis and eventual liver failure, make me want to explain the whole picture by a type of cirrhosis that developed in the course of recurrent cholangiolitic hepatitis. The concept of the recurrent type of cholangiolitic hepatitis and cirrhosis may not be generally acceptable but offers a good explanation of the sequence of events in this patient. I do not want to make a diagnosis of alcoholic cirrhosis, but we must admit that alcohol in some way influenced the liver damage. In other words, I do not believe that this picture will be that of alcoholic cirrhosis from the standpoint of the pathologist or a fatty type of liver. The liver tests indicated terminal liver damage. The severe jaundice and the elevation of prothrombin time associated with the hemorrhage, the positive cephalin-flocculation test and so forth enable one to say that the patient died in liver failure. He developed terminal uremia, and nothing more about that can be said other than that he probably developed bile nephrosis.

I should like to conclude that he had cirrhosis associated terminally with an acute hepatitis, cholangiolitic in type, bile nephrosis and liposarcoma of the spine and the psoas region. I cannot say whether or not this tumor invaded the region of the liver because I do not have the evidence to make such a statement.

Clinical Diagnoses

Cancer of liver.
Obstructive jaundice.

Dr. Clark's Diagnoses

Cirrhosis of liver.
Bile nephrosis.
Liposarcoma of spine.

Anatomical Diagnoses

Hepatoma, with invasion of cystic duct and metastasis to third lumbar vertebra.
Cirrhosis of liver.
Bile nephrosis.
Arteriosclerosis, generalized, moderate.

Pathological Discussion

Dr. Tracy B. Mallory: The slide of the biopsy in this patient was shown to a number of pathologists, and there was no general agreement concerning diagnosis. The outstanding feature of the histologic picture was a marked fatty vacuolization of the tumor cells, but on the other hand fat can be present in tumors for a number of reasons. The presence of fat does not prove that one is dealing with a liposarcoma. I did not see the slide until relatively recently and made a rather lucky guess on looking at it. I suggested that it might be a hepatoma. I know of a case in which the diagnosis of hepatoma was made from bone metastasis four years before the patient died and subsequently confirmed. In this case the interval was shorter but still significant — about two years.

Autopsy showed cirrhosis of the liver, which was rather finely granular in type, with a few large nodules and obvious invasion of the portal and hepatic veins with tumor thrombi — a characteristic behavior pattern of the primary liver-cell tumor. There was also involvement of the lymph nodes in the porta hepatis, from which the tumor had extended into the wall of the cystic duct and ulcerated so that fresh hemorrhage filled the biliary tract. The only other nodule of tumor found was in the lumbar vertebra, where it was originally seen by

x-ray study. It was by that time a rather large tumor mass, which had destroyed a large part of the vertebra and had extensively invaded the psoas muscle on one side. Microscopically, the tumor cells showed the usual arrangement seen in hepatomas, with numerous, huge tumor giant cells, which often contained 50 or 60 nuclei, a characteristic feature of primary tumor of the liver.

DR. CLARK: Metastatic hepatoma of the spine must be unusual. Would you say that that is true, Dr. Mallory?

DR. MALLORY: The major metastases of hepatoma are by way of the blood stream rather than the lymphatic vessels, although local lymph-node involvement may occur. The most frequent focus for metastasis under these conditions is naturally in the lungs. In this case the tumor seems to have passed through the lung without causing a gross lesion. Occasionally, as in hypernephroma, another blood-borne tumor, one sees similar bone metastases without demonstrable pulmonary lesions.

A PHYSICIAN: How often is this type of tumor found?

DR. MALLORY: We used to consider it very rare. Today it is not uncommon. There are parts of the world where it is one of the most frequent tumors, especially South Africa and Java. It is still relatively uncommon here. One almost never sees it except subsequent to a long-standing cirrhosis. I think that as our treatment of cirrhosis improves and we keep patients alive longer and longer, we shall see this tumor with progressive frequency.

DR. M. M. SUZMAN: In South Africa we have always found it associated with cirrhosis.

DR. MALLORY: The only other notable relation is with fluke infestation.

DR. WILLIAM MCK. JEFFRIES: Is hepatoma as radiosensitive as the tumor in this case?

DR. MALLORY: I cannot answer that. I do not believe that we have treated many hepatomas except in such terminal stages that there was no possibility of determining whether they were radiosensitive or not. Usually, by the time the diagnosis is made, the patient is almost moribund. Do you agree to that, Dr. Schulz?

DR. SCHULZ: I think that we treat them only by accident.

A PHYSICIAN: What is the explanation of the terminal uremia?

DR. MALLORY: That was a severe grade of bile nephrosis.

CASE 33442

PRESENTATION OF CASE

A forty-eight-year-old housewife was admitted to the hospital because of pain in the back and weakness of both legs.

The patient stated that as a young woman she had had pains in the lower back that sometimes limited activity. The pain was again pronounced when she was pregnant seventeen years previously. Beginning six and a half years before entry there was almost constant pain on the left side in the lower back, hip, anterior aspect of the thigh and leg, heel, sole of the foot and in all five toes. An operation for an intervertebral disk at the fourth and fifth lumbar region was performed five years before entry. The patient was free from pain until she started working again as a pianist, four months after the operation, when the same pain returned, steadily increasing in severity, and was shortly accompanied by some dragging of the left leg. One month before admission the right leg became weak. The weakness of both legs increased, and on admission the patient was able to walk only by using a cane and with the help of another person. Slight difficulty in voiding had been present for several days.

Physical examination revealed a well nourished woman in no obvious discomfort. The heart and lungs were normal. There was a low lumbar midline scar. Both legs were weak and spastic, the right more so than the left. The feet could be dorsiflexed just short of right angles. The knee jerk was absent on the left and present on the right. There was bilateral ankle clonus. Abdominal reflexes were absent, and ankle jerks were brisk; the plantar reflexes were extensor. Pain, touch and temperature sensation were impaired on the legs, posterior portions of the thighs and saddle area, but no sharply defined sensory level was demonstrated. There was diffuse tenderness over the lumbar spine and sacrum.

The urine had a specific gravity of 1.002, and the sediment contained occasional pus and epithelial cells. Examination of the blood disclosed 13.8 gm. of hemoglobin and a white-cell count of 8300.

A spinal puncture was performed in the third lumbar interspinous space. On jugular compression the pressure rose slowly from 150 to 350 mm. of water and fell very slowly to 250 mm. when compression was released. The protein was 204 mg. per 100 cc. X-ray examination showed an operative defect in the upper margin of the left lamina of the fifth lumbar vertebra, and degenerative changes about the smaller articulations between the fourth and fifth lumbar vertebras.

A myelogram was done on the second hospital day. The oil passed up to the body of the twelfth thoracic vertebra, where it was completely arrested, ascending slightly higher on the right and forming a fairly good "cap" (Fig. 1). On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR L. WATKINS: May we see the x-ray films?

DR. TOUFIC KALIL: There is no mention in the abstract of the fracture of the seventh thoracic

vertebra, and the myelogram shows this round irregular defect with complete blockage at the level of the twelfth dorsal vertebra. Reference to the other end of the Pantopaque column is seen here, with the block at the lower end, occurring at the fifth lumbar interspace, and with some irregularity of the lamina on the left, probably from the old operation.

DR. WATKINS: Do you see any evidence of destruction of the vertebra at the twelfth dorsal vertebra?

DR. KALIL: No.

DR. WATKINS: We have a history of intermittent complaints relative to the back, extending over a long period, with an increase in symptoms during pregnancy. The character of the pain became persistent about six and a half years before the final episode. At the time of the first operation there were sensory symptoms referable to the lower lumbar and first sacral segments, and presumably on this basis the operation was done for a protruding intervertebral disk. We do not have any further information about what was found, but we do know that as soon as activity was started again the pain returned, and for the first time we find evidence of definite involvement of the motor system, manifested by a dragging of the left leg. We should like to know what was the type of weakness — whether it was on the basis of anterior-root involvement, that is, the lower motor neuron type of weakness, or due to disease in the spinal cord, with some spasticity present; again, we can only guess about that. What finally brought the patient to the hospital was increase in pain and involvement of the opposite extremity.

Physical examination made it perfectly evident that we must go higher than the site of the previous operation to explain the physical signs: the spastic type of weakness, with Babinski response, ankle clonus and absent abdominal reflexes. A spinal puncture was done above the level of the previous operation, and there was block higher up as judged from the dynamics and also increased protein, so that we now look for a lesion in the lower part of the spinal cord. Although the sensory level was not very accurate, we suspect clinically from the physical findings involvement presumably of the first sacral segments, and we localize a lesion right at the end of the spinal cord to explain the present complaints.

Regarding the etiology of such a lesion, first of all we might consider the long history of back pain. This may simply have been a poor back mechanically. It is difficult to interpret from the x-ray film after the operations what sort of fault was present in the lumbosacral region. Frequently in pregnancy a patient with rheumatoid arthritis gets increase in back pain, but the sacroiliac films do not show any evidence of it, and we would expect after all these years to have definite x-ray evidence if it had been due to rheumatoid arthritis. This patient may have had pain for mechanical reasons and a ruptured disk to explain some of the symptoms, but the picture of a slowly increasing involvement of the spinal cord cannot be reasonably explained by a ruptured disk. I do not know how to link up what appears to be an old compression fracture in the dorsal area. We have no history of trauma above the level of the lesion that seemed to

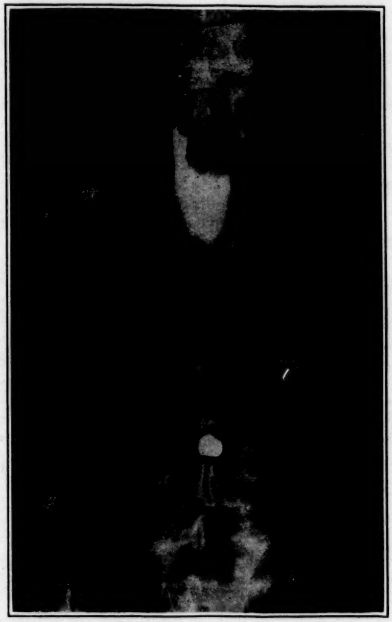

FIGURE 1.

be producing the symptoms, so that I am inclined to overlook that because there is no x-ray evidence of neoplasm.

Considering infection as a possible cause, we have nothing to suggest syphilis. Tuberculosis can of course cause spinal-cord compression, but if it were of such long standing we would expect a soft-tissue mass and some bony changes, which were absent, and I therefore think that we can rule out tuberculosis. Another possibility is arachnoiditis, which is sometimes given credit for intermittent and prolonged symptoms in numerous areas, but I would not expect it to cause an x-ray picture such as this, with so definite a block at one level. Again, arachnoiditis is not too satisfactory a pathological

diagnosis, and I do not believe that that is the answer in this case.

That leaves us with tumor of some sort as the most probable diagnosis. This was a slowly growing tumor with a history of at least six years' duration. If we localize it at the end of the spinal cord we can only guess what type of tumor it might have been. There is no evidence of metastatic disease or primary bone tumor, so far as I can see. I shall choose as my first guess an ependymoma of the conus or filum, which is slowly growing, or possibly a meningioma.

DR. AUGUSTUS ROSE: Do you think that she had a ruptured intervertebral disk?

DR. WATKINS: Yes, she may have had a ruptured disk, but I doubt whether it was responsible for the complaints, particularly if the weakness was spastic and developed immediately after operation.

DR. ROSE: Was a myelogram done before the operation for ruptured disk?

DR. CHARLES S. KUBIK: No; it was not.

Dr. Ballantine, will you describe the operative findings?

DR. H. THOMAS BALLANTINE, JR.: This patient was operated on under nitrous oxide, oxygen and ether anesthesia, and a laminectomy was done including the tenth, eleventh and twelfth dorsal vertebras just above the conus of the cord. The cord was found to be considerably widened, owing to diffuse swelling, more on the left than on the right, bearing out the x-ray findings that the block started slightly lower on the left side than on the right. I shall quote part of the operative note because it is interesting: "On opening of the dura the tumor could be seen bulging from the left posterior surface of the cord as a rounded purple-pink mass. There was considerable fusiform swelling of the cord above and below the tumor." The tumor seemed to start in the substance of the cord and seemed at first to be an intramedullary glioma, although against that was the fact that there was a discrete mass, which was removed almost as a dumbbell-shaped tumor. We got part of it out — a piece measuring about 1.5 cm. in diameter — and thought that that was all until further dissection showed below this layer another mass 2 cm. in diameter. At the time of operation there was no clue regarding the point of origin of this new tumor mass.

DR. KUBIK: What is the present condition of the patient?

DR. BALLANTINE: Postoperatively she had difficulty in voiding and marked increase in weakness in the legs. A week after operation these symptoms began to clear, and she developed fairly good tone in the right leg beginning at the ankle and the toes and some extension and dorsiflexion. The left leg was much slower in returning to normal. On intensive physiotherapy she reached the point where at discharge from the hospital, approximately a month later, she was able to bear weight on the left leg and quadriceps function was returning. I think that she will walk. The plantar signs cleared, and she had only occasional incontinence at night and was never incontinent during the day.

CLINICAL DIAGNOSIS

Tumor of spinal cord, eleventh dorsal region.

DR. WATKINS'S DIAGNOSIS

Ependymoma of conus?
Meningioma?

ANATOMICAL DIAGNOSIS

Meningioma of spinal cord.

PATHOLOGICAL DISCUSSION

DR. KUBIK: I suppose that it would be difficult to say whether or not this patient had a ruptured disk at the time of the original operation. The pain was the type caused by ruptured disk, and I should say less commonly observed with lesions as high as this. It seems likely that in this case the symptoms were caused by the tumor. The case illustrates the importance of careful clinical investigation.

DR. BALLANTINE: There is some evidence that this tumor was responsible for all the symptoms in that the back pain, of which the patient had complained for six and a half years, was relieved soon after the operation.

DR. KUBIK: The tumor was a meningioma. At operation it was thought that ependymoma was the more probable diagnosis. This is a common site for ependymomas, arising in the lower part of the cord or conus. Dr. W. Jason Mixter, as I understand it, did not find any attachment to the dura.

DR. BALLANTINE: No attachment was found.

DR. KUBIK: Histologically, the tumor was a typical meningioma.

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APPOINTMENT OF NEW EDITOR

The Committee on Publications of the Massachusetts Medical Society takes pleasure in announcing the appointment of Dr. Joseph Garland as Editor of the *New England Journal of Medicine*.

Richard M. Smith, *Chairman*

CHILD HEALTH SERVICE FOR STUDENT VETERANS

Plans for the care of approximately 1500 children of student veterans at Harvard have finally matured and were put into operation in mid-September. The project, which has been under consideration for a year or more, is based primarily on an urgent pediatric need. There have been at Harvard for the past two years, living in student housing facilities in Cambridge and at Harvardevens Village in Ayer, some 3000 GI families from all parts of the country, subsisting mainly on government allotments insufficient to provide adequate medical care for their children. This unusual concentration of infants and children, moreover, was beginning to overtax the medical facilities of the community and contained the possibility of serious difficulties in case disease should appear in epidemic proportions.

The need and the danger have been apparent to Dr. Arlie V. Bock, professor of hygiene at Harvard University, who enlisted the aid of Dr. Allan M. Butler, chief of the Children's Medical Service at the Massachusetts General Hospital and professor of pediatrics at Harvard Medical School. The plan that has gone into operation resulted.

Two health centers for the children involved have been opened, one in Cambridge and one in the Lovell General Hospital at Fort Devens. At these centers, under the direction of Dr. Francis C. McDonald, medical service, comprising physical examinations, immunizations, diagnosis and treatment, is being provided at federal expense. Home service is provided as needed, including consultation visits by pediatricians who are licentiates of the American Board of Pediatrics.

Harvard University provides clinic and office space, the Massachusetts General Hospital furnishes administrative services and clinical facilities and personnel, and the Massachusetts Department of Public Health aids in the administrative program, supervises the public-health nursing and provides consultative service on nutrition and medical social problems.

Last but not least, funds, based on a cost of $35 per patient per year are being provided by the Children's Bureau of the United States Federal Security Administration, via the Massachusetts Department of Public Health. These funds are available on the stipulation that they shall be used for a study as well as for a service project.

The service project has been outlined above. The study will consist largely in the collection and compilation of "statistics on the cost of providing complete health and medical care for infants and children as well as on the incidence of various illnesses and the kinds of service required." As such it should prove to be a valuable complement

to the survey of pediatric facilities of the country that has been undertaken by the American Academy of Pediatrics and is now drawing to its close.

There appears to have been launched, under excellent auspices, a particularly worthy government-financed project. Only one similar program has been conducted, that which was under way last year at the University of Washington, in Seattle. The medical profession at large should heartily approve of such a public-health and fact-finding undertaking.

STREPTOMYCIN IN BACTERIAL ENDOCARDITIS

Cases of bacterial endocarditis, irrespective of their etiology, were almost universally fatal prior to the introduction of the newer chemotherapeutic and antibiotic agents. The use of sulfonamides has resulted in cures only in rare cases. On the other hand, there is now a considerable body of evidence to show that penicillin is highly effective in the treatment of most cases of subacute bacterial endocarditis and has also produced cures in an appreciable proportion of cases of acute bacterial endocarditis due to penicillin-susceptible organisms.

There remains, however, a group of cases of acute and subacute bacterial endocarditis due either to streptococci that are relatively insensitive to penicillin or to gram-negative bacilli, which are quite resistant to the action of that antibiotic. Most of the latter organisms and some of the former are susceptible, at least in vitro, to streptomycin. It therefore seems reasonable to attempt prolonged and intensive streptomycin therapy in such cases.

The ease with which resistant variants appear in patients with various infections during the course of treatment with streptomycin, thus nullifying the effects of that antibiotic, and the nature of the lesion in cases of bacterial endocarditis may give rise to reasonable doubts concerning the effectiveness of prolonged and intensive treatment with streptomycin, particularly since irreversible deafness and vestibular damage occur in most cases. Such therapy can be justified, even in such a fatal disease, only if there is a reasonable expectation of cure of the underlying infection in a significant proportion of cases.

It is therefore gratifying to have a report summarizing the results of the use of streptomycin in the treatment of bacterial endocarditis. Hunter[1] reviewed the cases that have been treated at the Presbyterian Hospital, together with those collected by Dr. Chester S. Keefer and the Committee on Chemotherapeutic and Other Agents of the National Research Council. Of a total of 18 patients with bacterial endocarditis treated with streptomycin, 8 appeared to be cured. The cures included 4 of 8 cases in which a gram-negative bacillus was involved, 1 of 5 cases due to enterococci, 2 of 4 cases in which *Streptococcus viridans* was the organism and 1 case due to *Staphylococcus aureus*. Penicillin was also used, apparently without success, in the cases in which the gram-positive organisms were involved, and sulfonamides were used in some of the cases. One additional case of bacterial endocarditis due to a parainfluenza bacillus and apparently cured by streptomycin has recently been reported from the Massachusetts General Hospital.[2]

In some of the cases included in Hunter's report, failures were probably the result of treatment that was inadequate or was begun late in the course of the disease. The fact that an appreciable percentage of cases resulted in cures, however, indicates that streptomycin therapy is warranted in all cases of bacterial endocarditis due to gram-negative bacilli and in those due to other organisms that are sensitive to streptomycin in which the patient fails to respond to penicillin. The results in these cases also emphasize the importance of careful bacteriologic control in the management of such cases.

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2. Cases from the Medical Grand Rounds, Massachusetts General Hospital. *Am. Practitioner* 1:498-504, 1947.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

NELSON — Christian A. Nelson, M.D., of Cambridge, died on September 21. He was in his seventy-fourth year.

Dr. Nelson received his degree from Harvard Medical School in 1911. He was a former member of the Massachusetts Medical Society.

His widow survives.

UNDERHILL — Elizabeth C. Underhill, M.D., of Poughkeepsie, New York, died on September 20. She was in her seventy-seventh year.

Dr. Underhill received her degree from Cornell University Medical College in 1900. She was resident physician at Mt. Holyoke College for thirty-seven years.

ELLIOTT CARR CUTLER (1888–1947)

Elliott Carr Cutler was born in Bangor, Maine, on July 30, 1888, the son of George Chalmers Cutler and Mary Wilson Cutler. After his graduation *cum laude* from Harvard Medical School in 1913 he spent some months in Dr. Frank B. Mallory's laboratory, and then studied at the University of Heidelberg. He was surgical house officer at the Peter Bent Brigham Hospital from 1913 to 1915, and then resident surgeon at the Massachusetts General Hospital.

Dr. Cutler served in France in 1915, with the Harvard Unit, before the United States entered the war; his second tour of duty began in May, 1917, when he again went to France with Base Hospital No. 5. He was promoted to the rank of major in November, 1918, and received the Distinguished Service Medal.

On his return to the United States Dr. Cutler was resident surgeon at the Peter Bent Brigham Hospital from August, 1919, to September, 1921, associate in surgery at the hospital and chairman of the Department of Surgery, Harvard Medical School. In 1924 he was called to the professorship of surgery at Western Reserve University School of Medicine, Cleveland, where, in addition, he was director of the Surgical Service of the Lakeside Hospital. In 1932 he was chosen to succeed Dr. Harvey Cushing as Moseley Professor of Surgery at the Harvard Medical School and surgeon-in-chief of the Peter Bent Brigham Hospital.

Before the United States entered World War II, Dr. Cutler reorganized General Hospital No. 5, with which he had served in 1918. He was chief surgical consultant of the European Theater of Operations from August, 1942, to February, 1945, when he became Chief of the Professional Services Division in that Theater. He was promoted to a brigadier-generalship in June, 1945, and received an Oak Leaf Cluster to the Distinguished Service Medal already awarded. He was made honorary officer of the Most Excellent Order of the British Empire and received the *Croix de Guerre* with palm from the French Government and the Haakon VII Liberation Cross from the King of Norway.

At the time of his death he was president of the American Surgical Association — perhaps the highest honor that can be granted to any American surgeon. In 1947 he received the Bigelow Medal from the Boston Surgical Society. He was a member of the Society of Clinical Surgery, the New England Surgical Society, the American Association for Thoracic Surgery, the American Committee for the Protection of Medical Research, the Society for Experimental Biology and Medicine and the American Society for Clinical Investigation and honorary member of surgical societies of France, Italy and Belgium and was given honorary fellowships in the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh and the Royal Society of Medicine of England. He had received honorary degrees from the University of Strasbourg, the University of Vermont and the University of Rochester.

He was on the editorial boards of the *Journal of Clinical Investigation*, the *American Journal of Surgery*, the *American Heart Journal* and the *British Journal of Surgery*.

The obituary notice of the *British Medical Journal* (August 23, 1947) contained the following note, written by his friend and associate, Sir Gordon Gordon-Taylor: "Elliott had always driven the chariot of his busy, feverish life with rein unchecked; not one moment of the day wasted, no evenings 'steeped in honied indolence.' Even when the truth of his mortal illness came 'naked and sabre-like' against his great heart the pace of life never slackened. There was no neglect of the surgical direction of his hospital; he travelled all over the wide areas of the United States of America in his supreme desire that the surgical arrangements and the surgery for the veterans of the recent war should be the very best. The term 'deputy' found no place in his vocabulary. . . . No complaint of the unkind blow of Fate ever passed his lips; the courage of the man evoked admiration on every hand."

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Salem	November 3	Paul W. Hugenberger
Haverhill	November 5	William T. Green
Lowell	November 7	Albert H. Brewster
Brockton	November 13	George W. Van Gorder
Gardner (Worcester Subclinic)	November 18	John W. O'Meara
Springfield	November 18	Garry deN. Hough, Jr.
Pittsfield	November 19	Frank A. Slowick
Hyannis	November 20	Paul L. Norton
Worcester	November 21	John W. O'Meara
Fall River	November 24	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

CORRESPONDENCE

CONTRACEPTIVE CARE TO MARRIED WOMEN

To the Editor: An initiative petition seeking adoption of "An Act to Allow Physicians to Provide Medical Contraceptive Care to Married Women for the Protection of Life or Health" was filed the end of July, 1947, by the following petitioners: Karl T. Compton, president of Massachusetts Institute of Technology; Dr. Nathaniel W. Faxon, medical director, Massachusetts General Hospital; Dr. Robert H. Goodwin, obstetrician-in-chief, St. Luke's Hospital, New Bedford; Dr. Frederick C. Irving, professor emeritus of obstetrics, Harvard Medical School; Henry P. Kendall, of Sharon, president of Kendall Company; Dr. Samuel A. Levine, assistant professor of medicine, Harvard Medical School; Mrs. Arthur Devens Potter, of Greenfield, past president, Massachusetts State Federation of Women's Clubs; Dr. John C. Rock, clinical professor of gynecology, Harvard Medical School; Mrs. Arthur G. Rotch, former president of Massachusetts League of Women Voters; and Dr. George M. Shipton, chief of Obstetrical Department, House of Mercy Hospital, Pittsfield.

In submitting the petition, President Compton made the following statement:

> I believe that the public interest can best be served by placing in medical hands the control of medical matters. The giving of contraceptive care is a generally accepted medical technique which should not be denied by law to anyone whose medical need is great. Those needing and desiring contraceptive help should not be either left in complete ignorance or left at the mercy of irresponsible sources of information. Naturally, such information and help should not be forced upon anyone whose religious beliefs are opposed to those measures, but by the same token the religious beliefs of some should not be forced upon all. This is an elementary matter of civil liberties in a democracy.

With this statement I am in entire accord.

The petition has been approved by the Attorney General as to form and substance, and a minimum of 20,000 certified signatures of registered voters must be obtained this fall. The measure then goes to the Legislature, which must act by roll-call vote before June, 1948. If not enacted into law by the Legislature, the measure goes on the 1948 ballot as a referendum after the collection of a minimum of 5000 additional signatures.

A similar measure was rejected by a small margin of voters in 1942 after a vigorous campaign that aroused widespread interest and resulted in a larger number of votes being cast than on any previous referendum. At that time, the Massachusetts Supreme Judicial Court, in an advisory opinion, stated that such a measure was "purely permissive . . . (and) will not interfere with the freedom of any person within its scope to act in strict accordance with his religious views."

Only Connecticut and Massachusetts now prohibit doctors from prescribing contraception for their sick patients, although the American Medical Association and other medical groups have recognized the procedure as an integral part of preventive medicine.

I urge all physicians to support this measure and to help in obtaining the necessary number of signatures.

Robert L. DeNormandie, M.D.

Lincoln

NOTICES

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, November 6

Friday, November 7
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, November 10
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Wednesday, November 12
*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

October–December. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

November 6. New England Hospital for Women and Children. Page 650, issue of October 23.

November 10. Joint meeting of New England Society of Anesthesiologists and American Society of Anesthesiologists, Incorporated. Page 530, issue of October 2.

November 12. Division of Hospital Survey and Construction of the Massachusetts Department of Public Health. Page 650, issue of October 23.

November 13. Acute Myocardial Infarction. Dr. William M. Chambers. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

November 13–15. Association of Military Surgeons. Annual Meeting. Hotel Statler, Boston.

December 15–17. American Academy of Allergy. Page 602, issue of October 16.

February 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

March 28–April 4. American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.

April 19–23. American College of Physicians. Page xiii, issue of July 31.

May 6–8. American Association for the Study of Goiter. Page xiii, issue of July 31.

May 11–15. American Association on Mental Deficiency. Page 140, issue of July 24.

May 17–20. American Urological Association. Hotel Statler, Boston.

District Medical Societies

FRANKLIN
November 18.
January 13.
March 9.
May 11. Annual Meeting. Hotel Weldon.
All other meetings will be held at Franklin County Hospital.,

MIDDLESEX EAST
November 19.
January 21.
March 24.
May 12. Annual Meeting.
All meetings will be held at the Bear Hill Golf Club.

NORFOLK
November 25. Tufts Night.
January 27. Round-Table Discussion: Bleeding from the alimentary tract.
February 24. Obstetric and Gynecologic Night.
March 23. Harvard Night.

PLYMOUTH
November 20. Plymouth County Sanatorium, South Hanson.
January 15. Brockton Hospital, Brockton.
February 19. Toll House, Whitman.
March 18. Goddard Hospital, Brockton.
April 15. State Farm, Bridgewater.
May 20. Lakeville Sanatorium, Lakeville.

SUFFOLK
December 4. Censors' Meeting.

WORCESTER
November 12. Grafton State Hospital.
December 10. Worcester City Hospital.
January 14. St. Vincent's Hospital.
February 11. Worcester State Hospital.
March 10. Memorial Hospital.
April 14. Hahnemann Hospital.
May 12. Annual Meeting.